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The Efficacy of Swimming and Cycling Training in Individuals with Osteoarthritis: a Randomized Controlled Clinical Trial

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The Efficacy of Swimming and Cycling Training in Individuals with Osteoarthritis: a Randomized Controlled Clinical Trial

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Dissertation

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The Efficacy of Swimming and Cycling Training in Individuals with Osteoarthritis: a Randomized Controlled Clinical Trial

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Osteoarthritis (OA) is the number one cause of disability among older adults and is associated with cardiovascular disease (CVD) due, at least in part, to sedentary lifestyle in OA. Symptoms of OA such as joint pain act as a significant barrier for middle-aged and older adults attempting to perform physical activity. Thus, swimming can be an ideal form of exercise for patients with OA as it is non-weight bearing and would not aggravate symptoms of OA. However, there is no information available regarding the beneficial effects of regular swimming exercise involving patients with OA. Accordingly, the general aim of the present study was to determine the effects of a 12-week swimming exercise intervention on functional capacity, pain, vascular function, and markers of inflammation in middle-aged and older adults with OA. Using a controlled, randomized study design, forty-eight sedentary middle-aged and older adults with OA underwent 12 weeks of either swimming or cycling exercise training. Cycling exercise was used as a land-based exercise comparison group. All exercise sessions were closely supervised and consisted of 45 minutes/session 3 days/week at 60-70% heart rate reserve.

In Study 1, we assessed changes in functional outcomes and pain. Participants in both swimming and cycling exercise training groups demonstrated significant increases in distance covered during the 6-min walk test, as well as maximal grip strength and isokinetic knee extensor and flexor strength. We observed decreases in body mass, visceral adiposity, and waist and hip circumference in both exercise training groups. Additionally, there were reductions in pain and stiffness accompanied by increased physical function, as determined by the WOMAC index, in both groups. It should be noted, there was no advantage in the swimming or cycling group in any of these measurements.

In Study 2, we investigated improvements in vascular function and markers of inflammation. We observed significant reductions in central artery stiffness following both exercise interventions, and the arterial destiffening effects were observed all across various measures of arterial stiffness. A significant improvement in endothelium-dependent vasodilation, as determined by brachial flow-mediated dilation, was observed after the swimming, but not after the cycling exercise training. Furthermore, both exercise training groups significantly decreased levels of the inflammatory marker, IL-6. Taken together, results suggest that swimming exercise was effective in improving physical function and vascular function as well as in reducing pain in middle-aged and older adults with OA. These findings are of paramount clinical importance to patients with OA, as swimming may be a desirable mode of exercise, but is often viewed as inferior to land-based exercise in regards to maximizing health benefits gained from exercise.

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Chapter 1: General Introduction

Arthritis is a general classification for more than one hundred different types of degenerative joint diseases. According to a recent report from the National Health Interview Survey (NHIS), 50 million US adults (or 22% of the population) have been diagnosed with arthritis [1]. Among them, 21 million adults found themselves limited in their activities due to symptoms of arthritis [1]. It is estimated that by 2030, more that 67 million US adults will be diagnosed with arthritis [2-4]. The most common form of arthritis is osteoarthritis (OA) affecting nearly 27 million US adults. Not only is OA the most common form of arthritis, but is also the leading cause of disability in older adults, further contributing to a diminished overall quality of life [1]. Due to the inability to perform normal daily physical activity and side effects from pain medication, patient with OA are at greater risks of developing cardiovascular disease (CVD) and CVD-related mortality than the general population [5, 6]. Currently, there are no known cures or effective treatments for OA. From a societal standpoint, it is of paramount importance to investigate therapeutic approaches for the treatment of OA that are effective in reducing its symptoms, without increasing the risk of CVD.

The American College of Rheumatology recommends that aerobic exercise be included as part of the non-pharmacological treatment plan for pain and symptom management in OA patients [7]. Regular aerobic exercise is known to improve physical capacity and vascular function [8, 9] and appears to be very reasonable approach for OA

patients. However, the recommendation to increase aerobic exercise remains controversial and may be impractical, as the joint pain, stiffness, and functional limitations associated with OA reduce the ability to perform weight-bearing activities, even seemingly mundane activates like walking [10]. Under these circumstances, swimming may serve as an ideal form of aerobic exercise for OA patients. Middle-aged and older adults with OA often exhibit lower body orthopedic disability, bronchospasm, and heat disorders exercising in the heat. Swimming includes minimal weight-bearing stress, upper body exercise, a humid environment, and a reduced heat load. [11-13]. Although swimming seems to be an ideal exercise modality for patients with OA, no study has investigated the effects of regular swimming on functional capacities and vascular function in middle-aged and older adults with OA. A randomized clinical trial is needed to provide evidence of swimming as a safe and effective treatment for OA symptoms.

Research Purpose and Hypotheses

Study #1: The first study focused on the beneficial effects of swimming and cycling exercise interventions on functional capacity and pain rating in patients with osteoarthritis. This study used a controlled, randomized study design to determine the effects of swimming or cycling interventions. Supervised exercise training was performed for 45 minutes 3 days/week at 60-70% heart rate reserve for 12 weeks. The specific hypotheses were as follows:

Hypothesis #1: Both swimming exercise and cycling exercise would result in similar reduced pain and improved physical function and quality of life in middle-aged and older adults with osteoarthritis.

Hypothesis #2: Both swimming exercise and cycling exercise would result in similar improvements in muscular strength and mobility in middle-aged and older adults with osteoarthritis.

Study #2: The second study focused on the effects of swimming exercise and cycling exercise interventions on vascular function (i.e., central arterial stiffness and endothelial function) and blood markers of inflammation in middle-aged and older adults with osteoarthritis. This study used a controlled, randomized study design to determine the effects of swimming or cycling interventions. Supervised exercise training was performed for 45 minutes 3 days/week at 60-70% heart rate reserve for 12 weeks. The specific hypotheses were as follows:

Hypothesis #1: Both water-based and land-based exercise interventions (swimming and cycling) would result in similar improvements in vascular function in middle-aged and older adults with osteoarthritis.

Hypothesis #2: Both swimming exercise and cycling exercise will result in similar improvements in blood markers of inflammation in middle-aged and older adults with osteoarthritis

Chapter 2: Study 1 - Functional Capacity and Pain after Swimming and Cycling Training in Patients with Osteoarthritis

Abstract

Arthritis and its associated joint pain act as a significant barrier for middle-aged and older adults attempting to perform physical activity. Swimming can be an ideal form of exercise for patients with arthritis as it is non-weight bearing in nature. However, there is no information regarding the effects of regular swimming exercise on patients with osteoarthritis. The purpose of the present study was to determine the effects of a swimming exercise intervention on functional capacity and pain rating in patients with osteoarthritis. Using a controlled, randomized study design forty-eight sedentary middle-aged and older adults with osteoarthritis underwent either three months of swimming or cycling exercise training. Supervised exercise training was performed for 45 minutes 3 days/week at 60-70% heart rate reserve for 12 weeks. At baseline (before the exercise intervention), there were no significant differences in physical characteristics between the swimming and cycling exercise groups. There were significant reductions in pain and stiffness accompanied by increased reported physical function in both exercise groups. There were no significant group differences in the magnitude of the improvements. We concluded that swimming exercise was effective in improving function capacity and reducing pain associated with osteoarthritis in middle-aged and older adults with osteoarthritis. Additionally, the benefits of swimming exercise were similar to the more

frequently prescribed cycling training. This trial was registered at clinicaltrials.gov as NCT01836380.

Introduction

Osteoarthritis is the most common form of arthritis and is the leading cause of disability in older adults [14]. Because no cure is currently available for osteoarthritis, the treatment plan has focused on reducing pain and improving function while minimizing adverse effects. Although the American College of Rheumatology has recommended that aerobic exercise be included in the general osteoarthritis treatment plans [7], arthritis and its associated joint pain and stiffness act as a significant barrier for those attempting to perform land-based weight-bearing activity [10]. Additionally, the dogma that increased physical activity may result in greater wear-and-tear in already-affected joints remains a substantial concern for osteoarthritis patients [15-18]. Swimming appears to be the ideal form of aerobic exercise for middle-aged and older patients with osteoarthritis. The minimal weight-bearing stress facilitated by the buoyancy effects of water is an important element for patients afflicted with osteoarthritis that exhibit orthopedic problems affecting the hips and knees. Additionally, many osteoarthritis patients are obese and often suffer from heat-related problems when exercising in the heat. Swimming is characterized by a reduced heat load when participants are surrounded by water [11-13]. Because of these excellent traits of water-based exercise, swimming has been widely recommended for the treatment of osteoarthritis. Surprisingly, however, no study to date has been conducted to investigate the efficacy of swimming exercise training in patients with osteoarthritis. Thus, there is an urgent need to conduct randomized clinical trials to determine if swimming exercise is truly beneficial to patients with osteoarthritis.

Accordingly, the primary aim of the present study was to determine the effects of

3 months of swimming exercise training on physical function and pain in middle-aged and older patients with osteoarthritis. We included cycling training as a comparison groups as it is a land-based non-weight bearing exercise that has been shown to be effective in alleviating pain and improving function in patients with osteoarthritis [19-22]. Our working hypothesis was that both swimming exercise and cycling exercise would result in similar reductions in pain and improved physical function in patients with osteoarthritis.

Methods

Participants. Sedentary middle-aged and older adults (n=48) with Kellgren-Lawrence grade I-III radiographic osteoarthritis [23] were studied. Participants were recruited from orthopedic clinics and senior centers in the local community via flyers, e-mails, and information sharing and were screened for the study participation. Exclusion criteria were 1) having engaged in strenuous physical activity more than twice per week for the previous year [24], 2) unstable cardiac or pulmonary diseases, 3) joint replacement surgery during the past year, 4) intra-articular injection or systemic corticosteroid usage within the past six months, 5) severe disabling co-morbidity that would disallow receiving exercise therapy, and 6) aquaphobia. The Institutional Review Board at the University of Texas at Austin reviewed and approved the study. All volunteers gave their written informed consent before participation.

Exercise Training Intervention. Following baseline measurements, participants were randomly assigned to either swimming (n=24) or cycling (n=24) exercise training groups. Supervised exercise training conformed to guidelines established by the American College of Sports Medicine [25]. For the first few weeks, participants received active coaching and instruction by a member of the research team. Initially, participants exercised for 30 minutes/day, 3 days/week at an intensity exercise of 40-50% of heart rate reserve [HRR]. HRR was calculated using the equation: (maximal heart rate – resting heart rate) + resting heart rate. Age-predicted maximal heart rate was estimated using the new age-predicted equation [26]: 208 – 0.7 × age. As each participant's level of fitness improved, the intensity and duration of exercise increased with the goal of attaining 40-

45 minutes/day, 3 days/week at an intensity of 60-70% of HRR. Exercise training lasted 12 weeks. During the course of the investigation, participants were instructed to maintain their usual lifestyle and dietary habits.

The swimming training was performed in the swimming pools located in Gregory Gymnasium on The University of Texas at Austin campus. Water temperature of the swimming pool was held constant at 27–28 °C. The cycling training was performed on a stationary cycle ergometer in the Exercise Training Intervention Core Laboratory on The University of Texas at Austin campus. Each participant received instructions to exercise continuously except during the time needed for checking a target heart rate by heart rate monitor (Polar Electro, Lake Success, NY) secured on each participant's chest.

Testing Sessions. At baseline and post-intervention, measurements were performed in the same order and at the same time of day on each participant after having refrained from alcohol and exercise for at least 12 hours prior to their arrival. All prescription and over-the-counter medicines and supplements were identical for 7 days prior to the pre- and post-testing sessions. To avoid the acute effect of exercise, participants were studied at least 48 hours after their last exercise training session for the post-intervention testing session.

Body Composition. Height and body mass were measured with a physicians' balance scale (SECA, Hamburg, Germany). Body mass was measured while the participants were barefoot and in light clothing. Body mass index (BMI) was calculated using the equation: mass (kg) / height squared (m^2). Body fat percentage, lean tissue mass, and visceral adipose tissue were determined noninvasively using dual-energy x-ray

absorptiometry (iDEXA; GE Lunar Radiation, Madison, WI) [27, 28].

Mobility. Mobility was determined by having participants perform the 6-minutes walk test. Participants received instructions to walk as far as possible in 6 min on a flat, indoor surface and did not receive feedback or encouragement during the test but were allowed to rest if needed [29]. Footwear was recorded at the baseline testing session and replicated post-intervention. Additionally, during each testing visit participant was equipped with a pedometer (Omron HJ-324U) to assess the number of steps and stride lengths [30].

Muscle Strength. To determine upper-body muscular strength, maximal isometric grip strength of both arms was assessed unilaterally using a standard grip strength dynamometer. To determine lower-body muscular strength, isokinetic knee flexor and extensor strengths of both legs were assessed unilaterally at an angular velocity of 60 degrees/sec and 120 degrees/sec [31, 32] using a Biodex isokinetic dynamometer (Biodex Medical Systems, Shirley, NY). Participants were asked to cross their arms on their chest during testing, and no encouragement was provided. The reliability values ranged from 0.88- 0.97.

Pain and Disease Severity. Physical function and pain were evaluated using a self-administered questionnaire entitled the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The WOMAC consists of 24 items on a 5-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe, 4=extreme) that deal with participant's perception of pain, joint stiffness, and physical function. The WOMAC features five specific questions for pain that address sitting, lying in bed, walking, and ascending and

descending stairs. Scores for composite function ranged from 0-68, with higher scores indicating increased disease severity [33]. Based on our sample size, the minimal clinically important difference is 1.2 and 1.3 points (scale 0 to 10)[34].

Health-Related Quality of Life. Health-related quality of life was assessed with a validated self-report questionnaire, Short-Form Health Survey questionnaire (SF-36; Medical Outcomes Trust, Boston, MA) that consists of 36 questions that evaluate physical and mental health [35]. Based on our sample size, the minimal clinically important difference is 12 and 13 points (scale 0 to 100)[34].

Statistical Analyses. Data were analyzed using an intent-to-treat analysis [36] with a multiple imputation for all 48 randomized participants. To ensure the validity of the intention-to-treat analysis, we conducted per-protocol analysis of the 40 participants who completed the exercise intervention [37]. A two-way (time x group) repeated measures ANOVA was performed to compare outcomes of interest, with statistical significance set at an alpha-level of 0.05. When a significant main effect of time, treatment, or treatment x time interaction was detected, paired samples t-tests were used to assess intragroup differences at baseline and post. All statistical analyses including the imputation missing value were performed with SPSS Version 22.0 software (SPSS Inc, Chicago, IL). Data are presented as means±SEM.

Results

Selected participant demographic and clinical characteristics at baseline are presented in Table 1. Swimming and cycling groups were not different in age, sex distribution, and osteoarthritis-affected joints. Among the forty-eight participants randomly assigned to the groups, four participants in each group dropped out prior to the end of the intervention (Figure 1). The remaining participants had excellent compliance to swimming (98%) and cycling (97%) exercise training.

At baseline, there were no significant differences in physical and composition characteristics, and body stature between participants in the swimming and cycling exercise groups (Table 2). After the 12-week exercise intervention, body mass, visceral adiposity, and waist and hip circumference were decreased in both exercise training groups ($F= 12.561$, $p=0.001$; $F=12.779$, $p=0.001$; $F=24.437$, $p=0.001$; $F=17.952$, $p=0.001$, respectively). There were no significant group differences in the magnitude of the reductions between the two training groups.

As shown in Table 3, there were reductions in pain and stiffness accompanied by increased reported physical function, as determined by the WOMAC index, in both exercise groups ($F=29.246$, $p=0.001$; $F= 20.634$, $p=0.001$; $F=27.417$, $p=0.001$, respectively). Participants in both swimming and cycling exercise training groups demonstrated significant increases in distance covered during the 6-min walk test ($F=46.893$, $P=0.001$; Figure 4). Maximal grip strength and isokinetic knee extensor and flexor strength increased in both swimming and cycling exercise training groups ($F=4.251$, $p=0.039$; $F=19.246$, $p=0.001$; $F= 23.012$, $p= 0.001$, respectively; Figure 2 and

Figure 3). There were no significant group differences in the magnitude of the improvements.

Intention-to-treat analysis of 48 participants, including 8 drop-outs, was consistent with the per-protocol analysis of the 40 participants that completed the exercise interventions. Accordingly, we have only reported results from the intention-to-treat analysis.

Discussion

The present study is the first to demonstrate the benefit of swimming exercise training for treatment of osteoarthritis. Prior this study, swimming had been recommended by several medical organizations for the management of osteoarthritis [7, 38-41], but the efficacy of swimming in patients with osteoarthritis has never been studied. Prior to the present study, these recommendations had no scientific basis to support the claim. We found that three months of swimming exercise training produced improvements in physical function and pain in patients with osteoarthritis. Additionally, these changes were accompanied by the improvements in mobility, upper and lower body strength, as well as reductions in body mass, and joint stiffness. In general, the benefits gained from the water-based exercise were similar to cycling exercise training, the benefits of which are well established [19, 20].

Although no study had investigated specifically the efficacy of swimming exercise training in patients with osteoarthritis, several studies have compared aquatic exercises (e.g., water aerobics) to land-based exercises [42-45]. These studies found that both land-based and aquatic exercises reduced pain and improved physical function in patients with osteoarthritis. Although land-based exercise might be more convenient to perform, there may be psychological barriers to performing land-based exercise, as patients with osteoarthritis have enormous difficulty performing weight-bearing physical activity in their daily life due to the joint pain, joint stiffness, and muscle weakness [46-48] that could be aggravated by exercises, leading them to live a sedentary lifestyle [49, 50] or limit their daily physical activity to the minimum [51]. In light of this, water-based

exercises would be an ideal form of physical activity for patients with osteoarthritis due the minimal weight-bearing stress, humid environment, and reduced heat load [11-13]. Although swimming and aquatic exercise take place in water and are well received by patients with osteoarthritis, these water-based exercises differ significantly in regard to body position, muscle groups used, and sustainable exercise intensity. Further studies are needed to compare swimming and aquatic exercise or investigate the effect of the combination of swimming and aquatic exercise in treatment of osteoarthritis.

Most patients with osteoarthritis spend most of their time on land performing activities of daily living. Due to the principle of the specificity of exercise training [52], it was not known whether the functional benefits gained in water would be translated into the physical function in the normal daily life. In the present study, we assessed muscular strength, as determined by isokinetic quadriceps and hamstring strength and grip strength. Additionally, physical function, as determined by 6-min walk, distance improved significantly. Importantly, improvements in muscular strength and physical function achieved by swimming in water were similar to those elicited by cycling exercises performed on land. While improvements in muscle strength and the ability to perform physical activity are important, that arguably reductions in pain are equally important to physical function as pain is the primary barrier for performing physical activity in daily life in the first place. These results demonstrated that non-weight bearing exercise performed in water led to reductions in pain that patients with osteoarthritis experience while performing daily activities on land. The observed improvements in strength, physical function, and pain following non-weight bearing and non-specific exercise are

clearly important for further improvements and management of symptoms associated with osteoarthritis.

Although there were no significant differences between swimming and cycling exercise training groups, we stand to reason that this does not diminish the clinical importance of this study, but rather enhances it. A number of studies have shown a benefit of land-based exercise intervention compared with sedentary control conditions [53-56]. Moreover, several studies investigating the effects of regular exercise in patients with OA have also shown a benefit compared with sedentary control [19, 43, 57-61]. While we considered adding a sedentary control condition, we determined it to be unethical to forgo an effective treatment for patients with osteoarthritis. We are aware that some studies have used a waiting list-type sedentary control prior to entrance into the study [58, 60, 62] but decided against implementing it, as the integrity of a truly randomized study design, one of the most important aspects of any clinical trial, would have been lost with such study design. Thus, we decided to employ cycling as a land-based non-weight bearing exercise training comparison group since it has been shown to be effective in reducing pain, but more importantly is well-tolerated in patients with osteoarthritis [19-21].

There were several limitations of the present study. Participants only performed supervised exercise for 3 months. Although we observed health benefits of exercise training in this time span, it is unknown if continued participation in exercise training would maintain these benefits. An additional limitation is the lack of participant blinding to treatment allocation. Swimming is considered an ideal form of exercise for patients

with osteoarthritis. Placement in the alternate exercise condition may have affected self-reported outcomes or motivation. This is unlikely as they number of drop-outs were equal between exercise interventions. Lastly, we only included patients with mild-to-moderate radiographic OA. Not included were patients with advance stage of OA that were using a walker or were awaiting a joint replacement. Thus, we cannot generalize the present findings to that population. Future studies should investigate the benefits of exercise training in these patients, as they would likely benefit from swimming or cycling exercise program.

In conclusion, our results indicated that 3 months of non-weight bearing exercise training, including swimming and cycling, are effective in improving mobility, physical function, and upper and lower body strength, as well as reductions in body mass, pain, and joint stiffness in patients with osteoarthritis. Not only are these the first findings to indicate the efficacy of swimming exercise for patients with osteoarthritis, but they also demonstrate that swimming exercise exerts similar functional benefits to stationary cycling, a frequently-prescribed land-based aerobic training modality. Future studies should investigate if other benefits of swimming exercise (i.e., improved cardiovascular outcomes) are present after swimming exercise training in patients with osteoarthritis.

Table 2.1. Participant demographic and clinical characteristics.

Variables	Cycling	Swimming
Males/Females (n)	2/22	2/22
Age (years)	61 ± 1	59 ± 2
Race and ethnicity		
Caucasian, n (%)	18 (75)	16 (66.7)
African-American, n (%)	3 (12.5)	4 (16.7)
Hispanic, n (%)	3 (12.5)	3 (12.5)
Asian, n (%)	0 (0)	0 (0)
Other, n (%)	0 (0)	1 (4.2)
Affected joint		
Shoulder, n (%)	1 (4.2)	0 (0)
Hand, n (%)	2 (8.3)	1 (4.2)
Spine, n (%)	1 (4.2)	1 (4.2)
Hip, n (%)	3 (12.5)	2 (8.3)
Knee, n (%)	15 (62.5)	18 (75)
Foot, n (%)	2 (8.3)	2 (8.3)
Education (years)	16 ± 1	16 ± 1

Values are means ± SEM.

Table 2.2. Changes in selected participant characteristics.

	Cycling		Swimming	
Variables	**Before**	**After**	**Before**	**After**
Height (cm)	163±2	-	163±1	-
Body mass (kg)	84.5±3.8	83.0±4.1 *	92.0±4.7	89.4±3.9 *
Body mass index (kg/m^2)	31.6±1.7	31.0±1.9	34.6±2.1	33.9±1.7
Waist circumference (cm)	102±4	99±4 *	106±3	103±3 *
Hip circumference (cm)	116±3	114±3 *	120±3	117±3 *
Body fat (%)	44±2	44±2	45±2	44±2
Lean tissue mass (kg)	96±4	97±4	102±3	101±3
Visceral adipose tissue (kg)	3.3±0.4	3.2±0.4 *	3.4±0.3	3.0±0.3 *
Godin physical activity score (U)	15±2	35±1 *	13±1	38±2 *

Values are means ± SEM.
* $P<0.05$ vs. Baseline.

Table 2.3. Physical Function, Pain, and Health Related Quality of Life.

	Cycling		Swimming	
Variables	**Before**	**After**	**Before**	**After**
WOMAC				
Pain (0-20)	7.8±0.9	4.5±0.5 *	6.9±0.7	4.2±0.5 *
Stiffness (0-8)	4.4±0.4	3.1±0.3 *	3.8±0.3	2.6±0.3 *
Function (0-68)	23.5±1.8	17.5±2.7 *	20.9±2.1	11.7±1.9 *
Total (0-96)	35.6±3.4	21.5±4.7 *	31.5±2.6	18.4±2.6 *
Health-Related Quality of Life (SF-36)				
Mental score (0-100)	64±4	78±3 *	65±3	79±3 *
Physical score (0-100)	51±4	69±3 *	53±4	73±3 *

Values are means ± SEMs. WOMAC=Western Ontario and McMaster University Osteoarthritis Index
* $p<0.05$ vs. Baseline.

Table 2.4. Physical function and muscle strength tests.

	Cycling		Swimming	
Variables	**Before**	**After**	**Before**	**After**
Six-min walk test (m)	552±22	594±19 *	556±21	589±22 *
Six-min walk test (steps)	775±12	879±13 *	782±18	890±16 *
Walk speed (m/s)	1.5±0.06	1.7±0.06 *	1.5±0.06	1.6±0.1 *
Grip strength left (Kg)	21.8±1	23.0±1 *	20.6±1	21.3±1 *
Grip strength right (Kg)	22.8±1	24.6±1 *	20.2±1	20.6±1 *
Isokinetic knee peak torque at 60°/sec				
Right-extension (Nm)	62±5	72±5 *	58±4	68±4 *
Right-flexion (Nm)	41±4	50±3 *	42±3	50±3 *
Left-extension (Nm)	58±4	64±4 *	60±3	69±4 *
Left-flexion (Nm)	41±5	50±3 *	42±3	50±3 *
Isokinetic knee peak torque at 120°/sec				
Right-extension (Nm)	46±4	55±4 *	40±3	48±3 *
Right-flexion (Nm)	35±3	41±3 *	32±2	40±2 *
Left-extension (Nm)	44±3	53±3 *	44±2	56±3 *
Left-flexion (Nm)	35±3	40±3 *	33±2	44±2 *

Values are means ± SEM.
* $P<0.05$ vs. Baseline.

Figure 2.1. Participant flow through the trial.

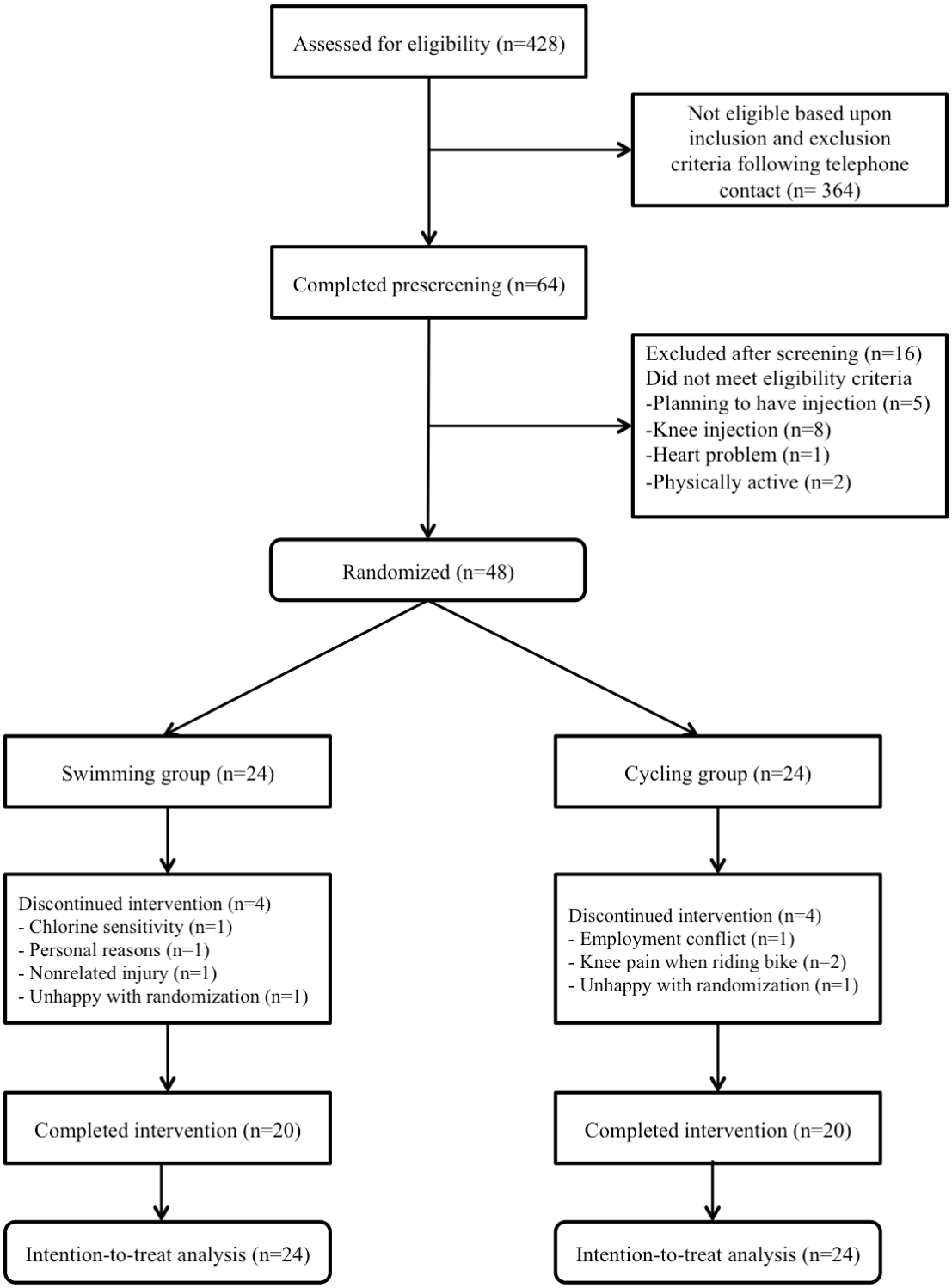


Figure 2.2. Isokinetic knee extensor and flexor peak torque at an angular velocity of 60 degrees/sec (Average right and left legs). * $P<0.05$ vs. Baseline. Values are means ± SEM.

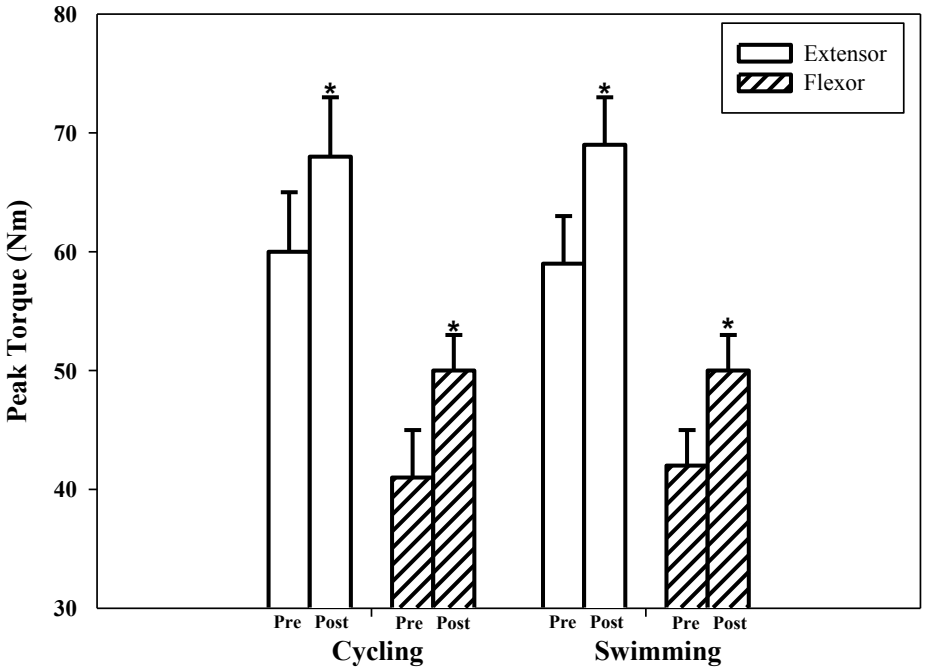


Figure 2.3. Isokinetic knee extensor and flexor peak torque at an angular velocity of 120 degrees/sec (Average right and left legs). * $P<0.05$ vs. Baseline. Values are means ± SEM.

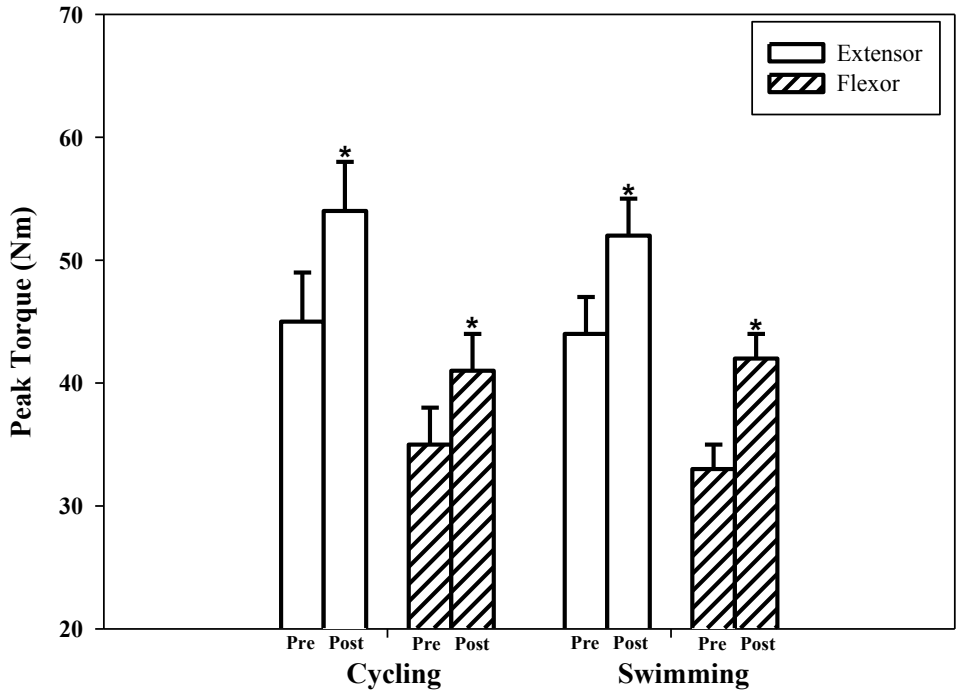


Figure 2.4. Six-minute walk test distance. * $P<0.05$ vs. Baseline. Values are means ± SEM.

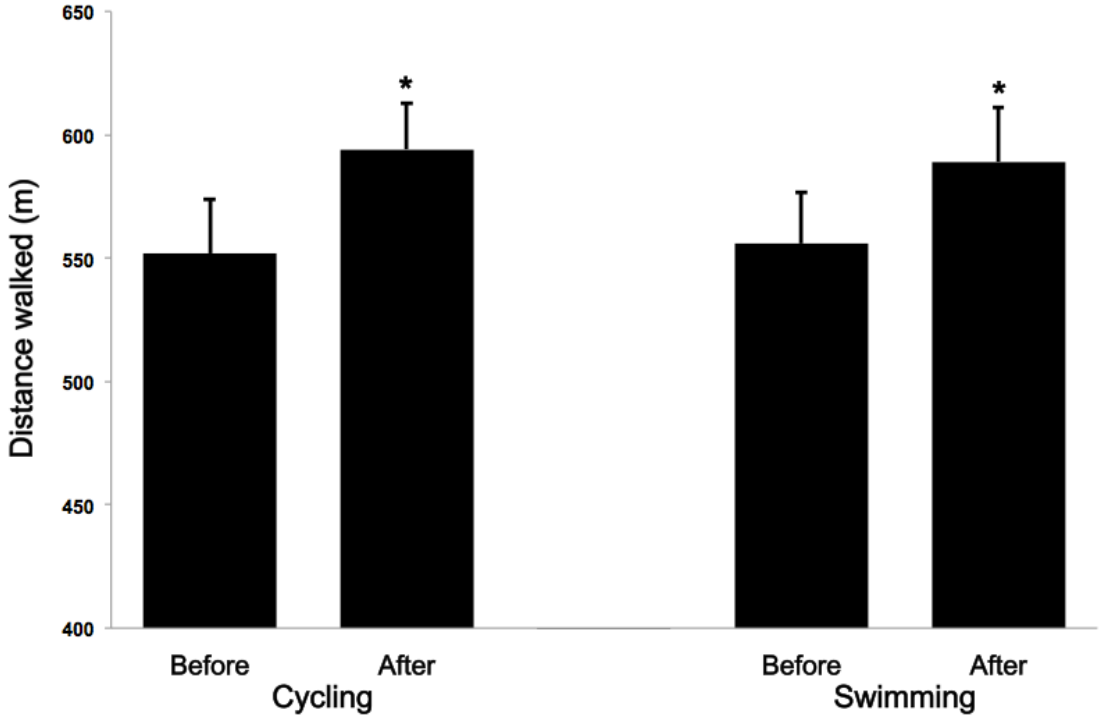
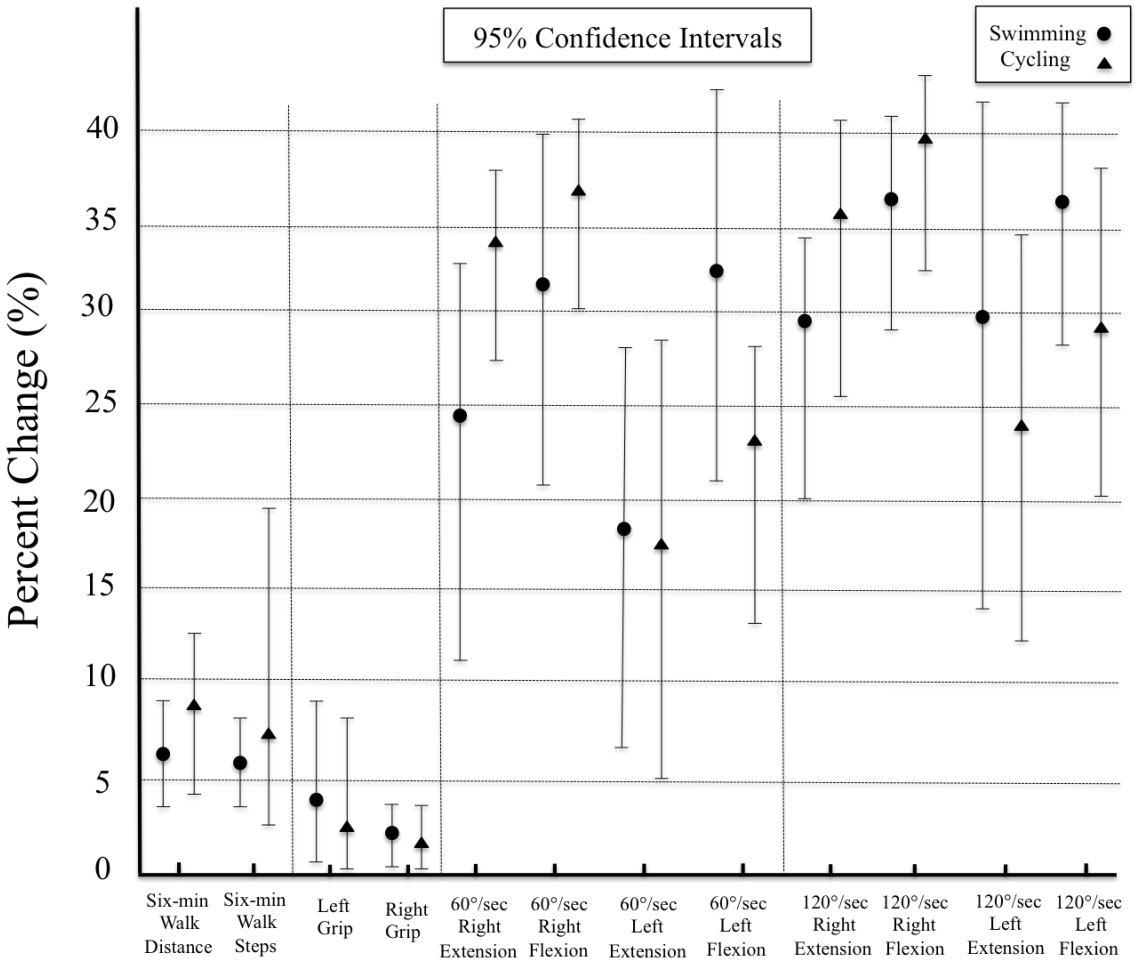


Figure 2.5. Pre-post percent changes in physical functions.



Chapter 3: Study 2 -Effects of Swimming and Cycling Exercise Interventions on Vascular Function and Inflammation in Middle-Aged and Older Adults with Osteoarthritis

Abstract

Osteoarthritis (OA) is the leading cause of disability in older adults and is associated with vascular dysfunction and low-grade chronic inflammation. Swimming exercise is an ideal and excellent form of exercise for patients with OA. However, there is no scientific evidence that swimming elicits similar benefits when compared with land-based exercises such cycling in terms of reducing vascular dysfunction and inflammation in individuals with OA. Forty-eight patients with OA were randomly assigned to swimming or cycling training groups. Cycling training was included as a non-weight bearing land-based comparison group. After 12-weeks of supervised exercise training, central arterial stiffness, as determined by carotid-femoral pulse wave velocity decreased significantly after both swimming and cycling training. Vascular endothelial function, as determined by brachial flow-mediated dilation, increased significantly after swimming, but not after cycling training. Both swimming and cycling reduced IL-6 levels. These results indicate that regular swimming exercise can exert similar or even superior effects on vascular function and inflammatory markers compared with land-based cycling exercise in patients with OA who often suffer from increased risk of developing CVD. This trial was registered at clinicaltrials.gov as NCT01836380.

Introduction

Individuals with osteoarthritis (OA) have higher rates of morbidity and mortality [14], due primarily to an increased risk of cardiovascular disease (CVD) [2, 63-67]. Although it is difficult to determine how OA increases the risk of CVD, increases in chronic inflammation and the sedentary lifestyle associated with OA may play an intricate role in increasing risk of CVD [68, 69]. Indeed, recent evidence indicates that vascular dysfunction, as assessed by increases in arterial stiffness and endothelial dysfunction may be potential mechanisms for the increased risk of CVD in OA [70, 71].

Regular aerobic exercise has been shown to reduce levels of inflammation, as well as improve markers of vascular function [8, 72-74]. Although exercise is typically recommended for patients with OA, the joint pain and stiffness associated with OA make it difficult to maintain even normal levels of physical activity [7, 75]. Accordingly, swimming is a form of aerobic exercise that encompasses minimal weight-bearing stress, upper body exercise, a humid environment, and a reduced heat load. [11-13]. For these reasons, swimming exercise may serve as an ideal form of exercise for patients with OA. In fact, swimming is universally recognized as an aerobic exercise, which is ideal for the prevention of cardiovascular disease and treatment for cardiovascular disease risk factors [9, 76, 77]. Interestingly however, there is no scientific evidence directly comparing swimming to land-based exercises such cycling in terms of reducing the risks of CVD in individuals with OA.

Accordingly, the primary aim of the present study was to determine the effects of swimming and cycling exercise interventions on vascular function (e.g. endothelial

function, central and local arterial stiffness/elasticity) and blood markers that pertain to inflammatory disease pathways of OA. The working hypothesis is that both swimming exercise and cycling exercise will result in improved central arterial stiffness and vascular endothelial function, and reducing inflammatory cytokine levels in middle-aged and older adults with OA.

Methods

Participants. A total of 48 previously sedentary middle-aged and older adults with osteoarthritis were studied. Participants were recruited from orthopedic clinics and senior centers in the local community via flyers, e-mails, and information sharing and were screened for the study participation. Exclusion criteria were 1) having engaged in strenuous physical activity more than twice per week for the previous year [24], 2) unstable cardiac or pulmonary diseases, 3) joint replacement surgery during the past year, 4) intra-articular injection or systemic corticosteroid usage within the past six months, 5) severe disabling co-morbidity that would disallow receiving exercise therapy, and 6) aquaphobia. The presence of osteoarthritis was confirmed by radiograph (Kellgren-Lawrence grade I-III) [23]. Institutional Review Board at the University of Texas at Austin reviewed and approved the study. All volunteers gave their written informed consent before participation.

Exercise Training Intervention. Following baseline measurements, participants were randomly assigned to either swimming (n=24) or cycling (n=24) exercise training groups. Supervised exercise training conformed to guidelines established by the American College of Sports Medicine [25]. For the first few weeks, subjects received active coaching and instruction by a member of the research team. Initially, participants exercised for 20-30 minutes/day, 3 days/week at an intensity exercise of 40-50% of heart rate reserve [HRR]. HRR was calculated using the equation: (maximal heart rate – resting heart rate) + resting heart rate. Age-predicted maximal heart rate was estimated using the new age-predicted equation [26]: 208 – 0.7 × age. As each participant's level of fitness

improved, the intensity and duration of exercise increased with the goal of attaining 40-45 minutes/day, 3 days/week at an intensity of 60-70% of HRR. Exercise training lasted 12 weeks. During the course of the investigation, participants were instructed to maintain their usual lifestyle and dietary habits.

The swimming training was performed in the swimming pools on The University of Texas at Austin campus. Water temperature of the swimming pool was held constant at 27–28 °C. The cycling training was performed on a stationary cycle ergometer in the Exercise Training Intervention Core Laboratory on The University of Texas at Austin campus. Each participant received instructions to exercise continuously except during the time needed for checking a target heart rate by heart rate monitor (Polar Electro, Lake Success, NY) secured on each participant's chest.

Testing Sessions. At baseline and post-intervention, measurements were performed in the same order and at the same time of day on each participant after having refrained from alcohol and exercise for at least 12 hours prior to their arrival. All prescription and over-the-counter medicines and supplements were identical for 7 days prior to the pre- and post-testing sessions. To avoid the acute effect of exercise, participants were studied at least 48 hours after their last exercise training session for the post-intervention testing session [78, 79]. All the image analyses were performed by an investigator who was blinded to the group assignment.

Body Composition. Height and body mass were measured with a physicians' balance scale (SECA, Hamburg, Germany). Body mass was measured while the participants were barefoot and in light clothing. Body mass index (BMI) was calculated

using the equation: mass (kg) / height squared (m^2).

Dietary Analyses. Subjects were given detailed instructions on how to keep 3-day dietary records by the research bionutritionist. Dietary records were collected before and at the end of exercise intervention and analyzed using Nutritionist Pro software (Axxya Systems, Stafford, TX). This software is based on the comprehensive food knowledge database with over 51,000 foods and ingredients.

Blood Pressure (BP) and Central Artery Stiffness. After ten minutes of supine rest, brachial and ankle BP, carotid and femoral pressure waveforms, and heart rate were simultaneously measured by an automated vascular testing device (VP-1000plus, Omron Healthcare, Kyoto, Japan) [80]. Carotid-femoral pulse wave velocity (cfPWV) was calculated as travel distance divided by the transit time as previously described [81]. Additionally, the right common carotid arterial diameter was imaged 1-2 cm proximal to the carotid bulb from the B-mode images on an ultrasound machine equipped with a high-resolution linear-array transducer (Philips iE33 Ultrasound System, Bothel, WA). An offline computer using automated image analysis software (Carotid Analyzer, Medical Imaging Applications, Coralville, IA) analyzed all images [82-84]. Analog output of carotid pressure waveforms was recorded (WinDaq 2000, Dataq Instruments, Akron, OH) for determination of central systolic BP and PP as well as for the subsequent determinations of carotid arterial compliance and distensibility, Young's elastic modulus, and ß-stiffness index as previously described [85].

Flow-Mediated Dilation (FMD). Brachial artery FMD was assessed after 10 min of supine rest using a Doppler ultrasound machine equipped with a high-resolution linear

array transducer (Philips iE33 Ultrasound System, Bothel, WA) positioned 5-10 cm proximal to the antecubital fossa [86]. After baseline arterial diameter determination, a pneumatic cuff positioned 3-5 cm distal to the antecubital fossa was inflated to >100 mmHg above resting systolic BP for 5 min (E20 Rapid Cuff Inflator, D.E. Hokanson, Bellevue, WA). To capture peak diameter, brachial artery diameter was monitored until three minutes past cuff deflation. Ultrasound-derived diameter data were analyzed using automated image analysis software (Brachial Analyzer, Coralville, IA).

Blood Inflammatory Markers and Chemistry**.** Blood samples were collected by venipuncture. Following centrifuging, serum and plasma were allocated into microcentrifuge collection tubes and stored at -80° C until biochemical analyses. Concentrations of 13 cytokines/chemokines involved in regulation of immune/inflammatory reactions were analyzed from serum samples using a Millipore multiplex bead array in a Bio-Plex 200 analyzer (Bio-Rad, Hercules, CA, USA). Fasting whole blood concentrations of total cholesterol, HDL-cholesterol, triglycerides, and glucose were determined enzymatically. LDL-cholesterol was estimated using the measured concentrations of total cholesterol, HDL-cholesterol, and triglycerides. Whole blood glycated hemoglobin concentration was measured using a commercially available glycated hemoglobin reagent kit (DCA Systems, Siemens Healthcare Diagnostics, Tarrytown, NY).

Statistical Analyses. Data were analyzed using an intent-to-treat analysis [36] with a multiple imputation for all 48 randomized participants. To ensure the validity of the

intention-to-treat analysis, we conducted per-protocol analysis of the 40 participants who completed the exercise intervention [37]. A two-way (time x group) repeated measures ANOVA was performed to compare outcomes of interest, with statistical significance set at an alpha-level of 0.05. When a significant main effect of time, treatment, or treatment x time interaction was detected, paired samples t-tests were used to assess intragroup differences at baseline and post. All statistical analyses including the imputation missing value were performed with SPSS Version 22.0 software (SPSS Inc, Chicago, IL). Data are presented as means±SEM.

Results

Baseline demographic and clinical characteristics are presented in Table 1. Swimming and cycling groups did not differ significantly in age, sex distribution, and osteoarthritis-affected joints. Among the forty-eight participants randomly assigned to the groups, four participants in each group dropped out prior to the end of the intervention. The remaining participants had excellent compliance to swimming (98%) and cycling (97%) exercise training.

As depicted in Table 2, physical and metabolic characteristics, body stature, and blood metabolic profiles did not significantly differ between participants in the swimming and cycling exercise groups at baseline. After the 12-week exercise intervention body mass decreased significantly in both exercise groups ($F= 12.561$, $p=0.001$).

There were no differences in supine BP measured in the brachial artery after either exercise intervention. However, central systolic BP and pulse pressure decreased significantly after both interventions ($F= 8.943$, $p=0.006$; $F= 20.769$, $p=0.001$, respectively; Table 3). The reductions in central BP were associated with reductions in central arterial stiffness as determined by cfPWV ($F=25.203$, $p=0.001$; Figure 2) and carotid artery compliance ($F=25.701$, $p=0.001$; Figure 3), carotid artery distensibility ($F=14.339$, $p=0.001$; Figure 4), and carotid β-stiffness index ($F=5.700$, $P=0.024$; Figure 5).

Moreover, changes observed in carotid pulse pressure after both exercise training were significantly related to changes in carotid artery compliance ($r=-0.43$), carotid artery

distensibility (r=-0.44), and cfPWV (r=0.31) ($p<0.05$ for all). Additionally, as depicted in Figure 6, endothelium-dependent vasodilatory function, as determined by brachial FMD, increased significantly after the swimming exercise ($F=12.478$, $p=0.001$) but not after the cycling exercise.

As depicted in Table 4, there were no significant differences in fasting blood lipid profile or glucose ($p>0.05$). However, there was a significant reduction in glycated hemoglobin in both exercise training groups ($F=5.168$, $p=0.042$). Additionally, there were significant reductions in plasma cytokine concentrations of IL-6, a marker of inflammation, in both exercise training groups ($F=9.352$, $p=0.005$; Table 4).

Intention-to-treat analysis of 48 participants, including 8 drop-outs, was consistent with the per-protocol analysis of the 40 participants that completed the exercise interventions. Accordingly, we have only reported results from the intention-to-treat analysis.

Discussion

The prominent findings of the present study are as follows. 1) We observed significant reductions in central arterial stiffness following both exercise interventions, and the arterial destiffening effects were observed across all measures of arterial stiffness. 2) Central systolic BP and pulse pressure decreased significantly with both exercise interventions whereas peripheral (brachial) BP did not change in either intervention. 3) An improvement in endothelium-dependent vasodilation was observed after the swimming but not after the cycling intervention. 4) Both exercise training intervention decreased levels of the inflammatory marker, IL-6. These results indicate that regular swimming exercise elicits beneficial improvements in vascular function and inflammation in patients with OA and that these benefits induced by the water-based exercise are similar to or even better than a land-based exercise. To the best of our knowledge, this is the first study to determine the effect of swimming exercise intervention on improvements in vascular function and inflammatory markers in patients with OA.

Osteoarthritis is the number one cause of disability among older adults, and a growing body of evidence indicates that OA is strongly associated with CVD [2, 63-67]. Recently, it was observed that patients with OA have a higher level of central arterial stiffness, as measured by PWV [70], as well as endothelial dysfunction, as determined by FMD [71]. In the present study, we observed significant reductions in cfPWV and other measures of arterial stiffness after both exercise interventions. Additionally, we observed improved endothelial function, as determined by brachial FMD, in the swimming group,

but not in the cycling group. A possible explanation for this finding is unknown but might be related to the principle of the specificity of exercise training [87]. Unlike cycling exercise that relies on legs, swimming is mostly an upper body exercise performed in water. Since FMD was performed on brachial artery in the arm, the vascular effect may have manifested only in the upper body exercises (i.e., swimming). Regardless of the mechanism for increased FMD, the present findings indicate that swimming may be more effective in reducing the risk of future CVD, as indicated by the sole improvement in FMD.

Peripheral BP measured at the brachial artery did not change after either intervention. However, central systolic BP and pulse pressure were reduced significantly after both exercise training interventions. In recent years, central BP, particularly pulse pressure, has gained attention among clinical investigators [88], as it has been shown to be more predictive of risk of future CVD and CV events than peripheral BP measurement [89]. Indeed, BP lowering drugs that reduce central and peripheral BP tend to have a greater benefit than those that only reduce peripheral BP alone [89]. Reductions in central BP, but not peripheral BP, might be puzzling but can be explained by changes in central arterial stiffness having a greater influence on central BP. Indeed, we observed significant associations between changes in central arterial stiffness and changes in central BP in the present study. These findings indicate that reductions in central arterial stiffness following aerobic exercise may improve future risk of CVD in patients with OA in multiple ways, as they appear to be related also to changes in central BP.

Regular exercise is universally recommended by clinicians as a form of treatment

to manage symptoms of OA, such as pain [7, 38, 40, 90] and to improve CVD risk profile [8, 74]. Regular aerobic exercise reduces specific inflammatory markers related to CVD, and these markers may also be relevant to the OA disease progression pathway [72, 73]. Indeed, inflammation plays a role in OA pathogenesis [91] and is suggested to act as a trigger for many symptoms of osteoarthritis, including joint pain, swelling, and stiffness [92]. Additionally, patients with OA demonstrate higher levels of systemic inflammation markers [69]. In the present study, we observed significant reductions in the inflammatory cytokines, IL-6, following 12-weeks of swimming and cycling exercise. These findings provide evidence that exercise in patients with OA could aid in the treatment of OA through reductions in chronic inflammation.

In conclusion, the present study is the first to demonstrate beneficial effects of swimming and cycling exercise on improving vascular function in patients with OA. While both exercise interventions were successful in decreasing central arterial stiffness, only swimming exercise was able to improve vascular endothelial function. These findings are of paramount clinical importance to patients with OA, as swimming is a desirable mode of exercise, but is often viewed as inferior to land-based exercise in regards to maximizing health benefits gained from exercise.

Table 3.1. Changes in selected participant characteristics.

	Cycling		Swimming	
Variables	**Before**	**After**	**Before**	**After**
Height (cm)	163±2	-	163±1	-
Body mass (kg)	84.5±3.8	83.0±4.1 *	92.0±4.7	89.4±3.9 *
Body mass index (kg/m^2)	31.6±1.7	31.0±1.9	34.6±2.1	33.9±1.7
Total caloric intake (kcal/day)	1,831±160	1,864±175	1,856±167	1,894±179
Protein intake (g)	80±7	82±6	79±6	78±7
Fat intake (g)	73±9	78±6	72±5	74±6
Carbohydrate intake (g)	196 ± 15	199±11	189 ± 11	195 ± 12
Alcohol intake (g)	9±2	6±4	11±6	10±7
Godin physical activity score (U)	15±2	35±1 *	13±1	38±2 *

Values are means ± SEM.
* P<0.05 vs. Baseline.

Table 3.2. Casual blood pressure and cardiovascular measurements.

	Cycling		Swimming	
Variables	**Before**	**After**	**Before**	**After**
Systolic BP (mmHg)	126±3	120±2	120±3	120±4
Mean BP (mmHg)	94±2	91±2	89±2	89±3
Diastolic BP (mmHg)	79±2	77±2	74±1	74±2
Pulse pressure (mmHg)	47±2	45±2	45±3	46±3
Central Systolic BP (mmHg	105±8	100±9 *	100±8	97±11*
Central Pulse Pressure (mmHg)	27±4	24±4 *	29±6	26±5 *
Heart rate (bpm)	68±2	68±2	67±2	62±2
Pulse wave velocity (cm/sec)	1,201±34	1,103±35 *	1,287±32	1,194±36 *
Flow-mediated dilation (%)	2.9±0.6	3.3±0.6	3.0±0.7	6.0±0.4 *
Carotid artery compliance (mm^2/mm Hg)	0.188±0.01	0.229±0.01*	0.170±0.02	0.213±0.01*
Carotid artery distensibility ($mm\ Hg^{-1}$)	8.08±0.8	9.83±1.3*	6.45±0.4	8.22±0.5*
Carotid β-stiffness index (AU)	9.80±0.6	8.88±0.4*	12.84±1.2	9.92±0.8*
Carotid artery IMT (mm)	1.4±0.4	1.2±0.4	1.2±0.4	1.2±0.3

Values are means ± SEM. BP= Blood Pressure, IMT= Intima-Media Thickness
P<0.05 vs. Baseline.

Table 3.3. Blood concentration of cardiovascular risk factors and inflammatory markers.

	Cycling		Swimming	
Variables	**Before**	**After**	**Before**	**After**
Total cholesterol (mmol/L)	5.4±0.2	5.3±0.2	4.9±0.2	4.7±0.2
HDL-cholesterol (mmol/L)	1.6±0.1	1.6±0.2	1.6±0.1	1.6±0.1
LDL-cholesterol (mmol/L)	3.2±0.2	3.3±0.3	2.8±0.1	2.7±0.1
Triglyceride (mmol/L)	1.3 ±0.1	1.0±0.1	1.2±0.1	1.1±0.1
Glucose (mmol/L)	5.1±0.1	5.1±0.4	5.4±0.1	5.4±0.1
HbA1c (%)	5.7±0.1	5.6±0.1*	5.7±0.1	5.6±0.1 *
Interleukin-1 beta (pg/mL)	57±9	48±8	38±5	37±4
Interleukin-2 (pg/mL)	56±10	71±10	49±9	41±8
Interleukin-4 (pg/mL)	45±7	38±4	45±7	36±4
Interleukin-5 (pg/mL)	62±5	57±6	39±3	39±4
Interleukin-6 (pg/mL)	90±10	79±9*	100±11	76±7*
Interleukin-7 (pg/mL)	53±6	48±6	45±5	42±6
Interleukin-8 (pg/mL)	260±34	275±35	225±22	241±14
Interleukin-10 (pg/mL)	152±43	155±46	105±7	95±7
Interleukin-12 (pg/mL)	48±8	53±10	48±10	41±7
Interleukin-13 (pg/mL)	50±10	46±7	37±6	31±3
IFN-gamma (pg/mL)	46±4	44±7	54±9	49±7
TNF-alpha (pg/mL)	264±26	253±25	246±23	236±23

Values are means ± SEM. HbA1c= Glycated hemoglobin, IFN= Interferon, TNF= Tumor necrosis factors. * $P<0.05$ vs. Baseline.

Figure 3.1. Changes in central arterial stiffness as assed by carotid-femoral pulse wave velocity (cfPWV). * $P<0.05$ vs. Baseline. Values are means ± SEM.

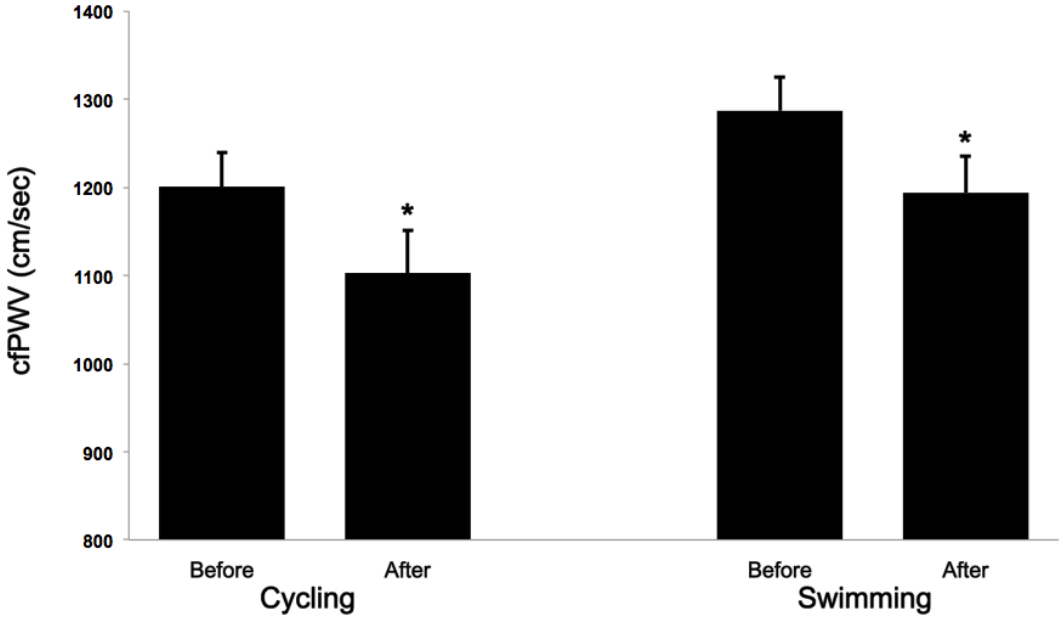


Figure 3.2. Change in carotid artery compliance. * $P<0.05$ vs. Baseline. Values are means ± SEM.

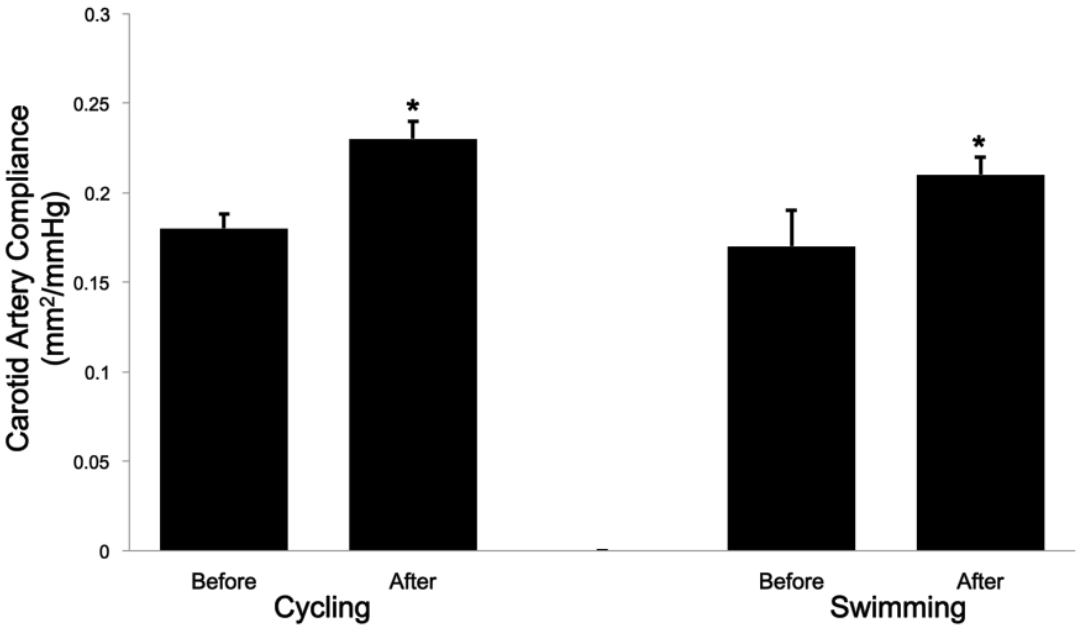


Figure 3.3. Change in carotid artery distensibility. * $P<0.05$ vs. Baseline. Values are means ± SEM.

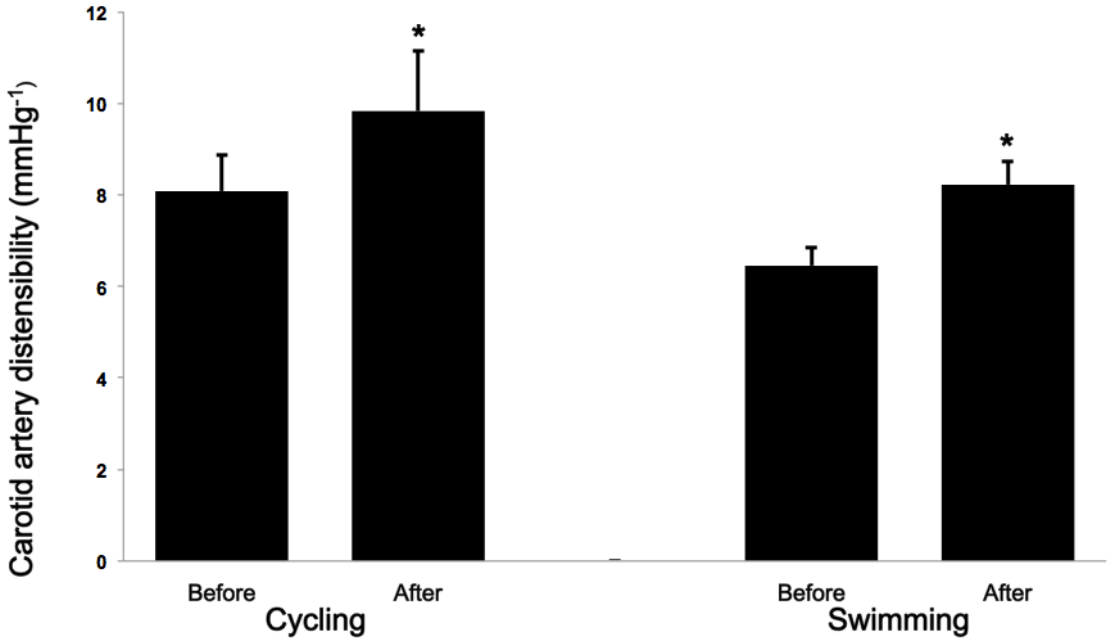


Figure 3.4. Change in carotid β-stiffness index * $P<0.05$ vs. Baseline. Values are means ± SEM

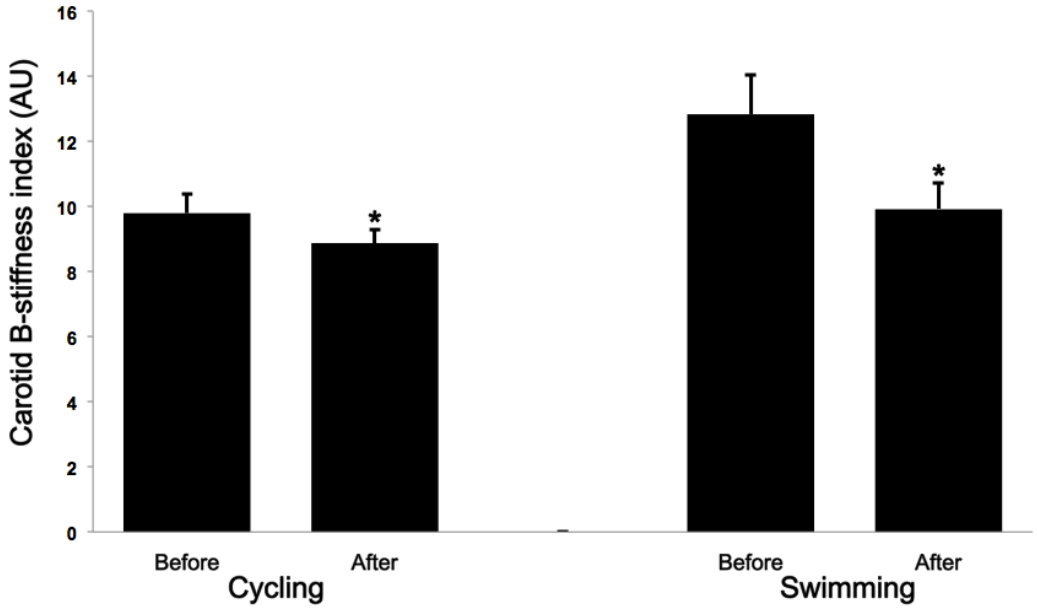
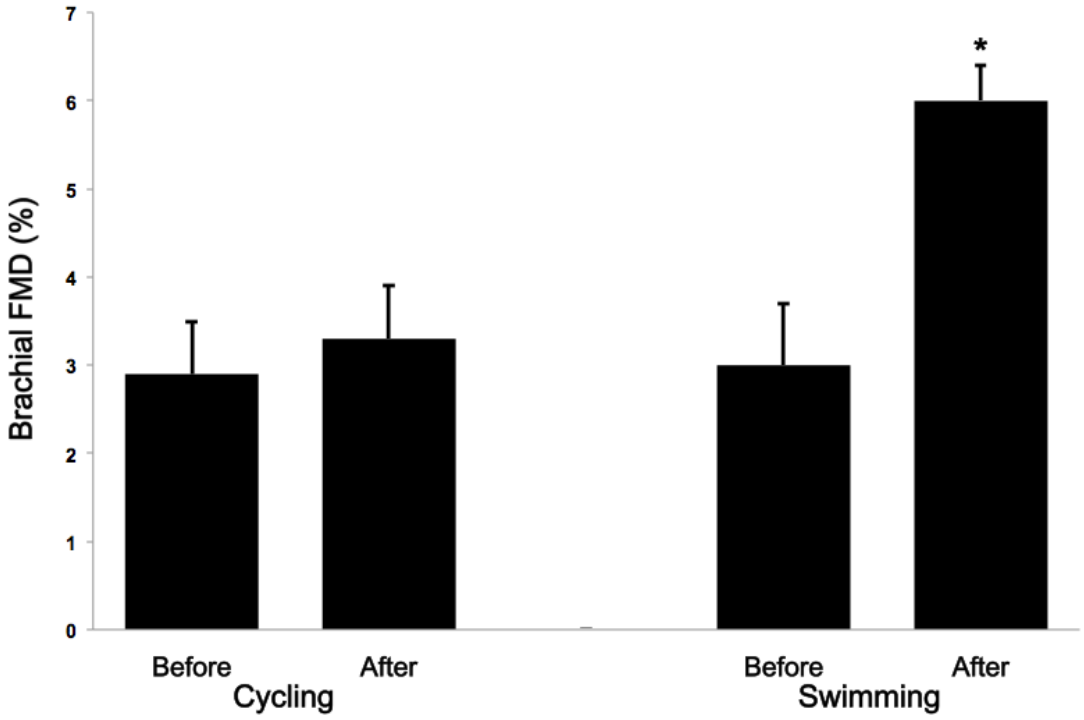


Figure 3.5. Change in endothelium-dependent vasodialation as assessed by Brachial Flow-Mediated Dilation (FMD). * $P<0.05$ vs. Baseline. Values are means ± SEM.



Chapter 4: Review of Literature

Osteoarthritis (OA) is a chronic disease that ranks as the most common form of arthritis. Osteoarthritis arises when biomechanical and biochemical changes become pathological in their interconnected destruction of articular cartilage and subchondral bone. This insidious deterioration can result in erosions of the bone and cartilage, and the formation of osteophytes and subchondral cysts that consequently give rise to joint pain, joint space narrowing, and varying degrees of low-grade inflammation processes [93]. Pain and functional limitations due to OA are reported in 13% of Americans between the ages of 55-64 and 17% of Americans ages 65 to 74 [49]. Overall, OA affects nearly 27 million American adults over the age of 25 years [4], making it the most common cause of chronic disability in older adults with two-thirds of adults over the age of 65 afflicted [94].

There are a number of modifiable risk factors that contribute to development of OA such as overweight and obesity, occupation, and previous joint trauma. In addition to the modifiable risk factors, there are some non-modifiable factors that have been shown to be associated with a greater risk of OA like aging, gender, and family history [93, 95-98]. While the most commons symptoms of OA are pain and/or crepitus during movement, tenderness, and malalignment or joint deformity [93], other symptoms of OA are typically present as a compilation of symptoms including joint pain, stiffness, swelling, loss of function, bony sclerosis, joint space narrowing, and decreased range of motion. Osteoarthritis can be present in any joint, but most commonly affects the feet,

knees, and hips, all of which are weight bearing joints. As such, OA patients may have extreme difficulty and pain with activities of daily living including walking, climbing stairs, and kneeling [10], thus, many OA patients eventually opt for total hip and knee replacements.

Pathogenesis and Risk Factors for Osteoarthritis

Natural biological and physiological processes constantly remodel human articular cartilage through anabolic and catabolic processes. In normal cartilage, a balance exists between the synthesis and deterioration of extracellular matrix components. However, articular cartilage in OA fails to maintain this process where new matrix synthesis overpowers matrix [97]. Increased matrix catabolism is commonly attributed to the up-regulation of proteinase activities, especially collagenases, gelatinases, and stromelysisn. These enzymes degrade collagen and other matrix components [99]. Analysis of synovial fluid shows higher concentrations of collagenases, gelatinases, and stromelysisn in OA subjects compared with normal controls [99, 100]. Thus, osteoarthritis is considered a disease confined to articular cartilage associated with osteophytes and bony sclerosis [10].

Although the exact cause of OA has not yet been determined, there are several risk factors that play a crucial role in the etiopathogenesis and development of OA [4, 49, 93, 94, 96, 97]. A primary risk factor for OA is aging, as such the prevalence of OA increases from 50% of the population at age 65 to more than 85% at age 75 [4, 101]. Women are at higher risk of OA compared with men. The increased prevalence of OA in

women is primarily mediated by menopause [100]. A body mass index classification of overweight or obese is considered to be another major risk factor for developing arthritic knees [102]. In fact, people who have a body mass index (BMI) of 30 to 35 kg/m^2 (Obesity I) are nearly four times as likely to developing knee OA compared with people classified as normal BMI (25 to 29 kg/m^2) [102]. Overall, these risk factors all tend to have aging in common. Although aging cannot be prevented, the deleterious and disabling side effects associated with OA may be prevented or treated by reducing the impact of modifiable risk factors associated OA that can increase with age.

Osteoarthritis and Cardiovascular Disease

Cardiovascular disease (CVD) is the number one cause of death in the US [103, 104], and risk factors related to OA are highly predictive of future CVD. For example, coronary heart disease, heart failure, and stroke. Additionally, OA itself increases the risk of future CVD due to the reduced physical activity and unavoidable adoption of a sedentary lifestyle due to joint pain and discomfort observed in OA [105, 106]. Moreover, recent studies have indicated that immobility due to the pain resulting from arthritis leads to frailty and muscle weakness which may further increase CVD risk [107]. It has been established in the last 50 years that individuals with OA are at higher risk for CVD events than the general population [5, 64, 108, 109]. In one recent prospective longitudinal study that randomly selected and followed 600,000 patients for 18 years observed that OA increased the risk of hospitalized CVD in older women (17%) and in older men (15%). Additionally, these patients with OA had increased risk of ischemic

heart disease (IHD), congestive heart failure (CHF), and myocardial infarction (MI) [64]. Thus, it is reasonable to hypothesize that reductions in risk factors that are predictive of future OA may indirectly, as well as directly reduce the risk of future CVD.

There are many other risk factors for CVD including demographic, social, and behavioral factors, including but not limited to age, gender, body weight, hypertension, dyslipidemia, diabetes, income, ethnicity, smoking, and diet [103, 104, 110]. But recent studies have emphasized the importance of systemic inflammation in increasing the risk of future CVD [111, 112]. Patients with rheumatic diseases, such as rheumatoid arthritis, psoriatic arthritis, and systematic lupus erythematosus, are characterized by chronic low-grade inflammation and are at greater risk of CVD and CVD-related mortality compared with healthy adults [112]. Although these conditions represent a diseased state, chronic low-grade inflammation (e.g., elevated C-reactive protein or CRP, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)) in seemingly healthy individuals is also implicated in increases risks of a premature CVD-related death [113, 114].

Patients with OA have a higher risk of mortality compared to people without OA due to the presence of either one or a combination of the following: CVD, diabetes mellitus, dementia, and cancers in comparison to the general population [66, 115]. Much of the research elucidating the relationship between OA and CVD has been through prospective longitudinal studies [64, 109]. Even though physicians often define OA as a degenerative disease, inflammatory mechanism plays a significant role in the development and progression of OA [92]. Thus, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly administered for the treatment of inflammation and other

symptoms related to OA. However, long-term NSAID use may not be ideal as it is associated with an increased risk of CVD [2]. In addition, as OA progresses in its onset, severe pain in the joints arises, thus rendering patients less physically active, when compared with individuals without arthritis [4]. Accordingly, it is generally stated that patients with OA experience elevated risk of CVD due to a systemic chronic inflammation reduced physical activity, and sedentary lifestyle.

Role of Vascular Function and Cardiovascular Disease

Impairments in vascular function greatly increase the risk of future CVD [116-118]. There are a number of elements in vascular function, but the most commonly studied aspects are those of large elastic arteries that can be measured noninvasively via ultrasound and applanation tonometry [119]. One of the most important aspects of vascular function is the stiffness of the central arteries. In young individuals, these arteries are highly elastic. As people get older, the central arteries in the body get stiffer since their elasticity significantly lessens. Consequently, this occurrence increases the body's blood pressure and puts an individual's risk of developing cardiovascular disease plus other heart related conditions [120, 121]. One of the primary roles of the central arteries is to control the movement of blood which gets pumped out through the heart's left ventricle with each cardiac cycle. For a normal working cardiovascular system, the capacity to control the blood is very important because with each stroke, adequate amounts of blood can be ejected while at the same time maintaining low pressure on the ventricle [119]. This function is best observable when a person is exercising, more blood

is getting in and out of the heart through the ventricle but the central arteries control the blood movement by adjusting to the volumes of blood being ejected from the heart. Contrary to older arteries, young arteries are much more elastic and with each cardiac pulsation the arteries are able to expand and shrink back with relative ease [122, 123]. Over time, the central arteries become stiffer and as a result the heart has to work harder because the blood is not flowing in and out with ease. Consequently, this occurrence is a precursor to Left Ventricular Hypertrophy (LVH) and adversely, LVH is a potent forecaster of unpleasant cardiovascular conditions [124]. In fact, with LVH, the central arteries get stiff which results in more velocity as blood begins to travel through the arteries with alarming pressure [125].

Increases in stiffness can be measured by determining the velocity at which the pulse waveform travels through the arterial tree (Pulse wave velocity; PWV) [119]. In young elastic arteries, the pulse wave travels slowly, while in older stiffer arteries, PWV increases substantially. Aortic PWV can be assessed non-invasively by determining the transit time it takes the pulse waveform to travel between the carotid and femoral arteries. Measurement of pulse wave velocity through this method is considered the gold standard for measurement of central arterial stiffness and is highly predictive of future cardiovascular events [116, 126]. Another measurement of central arterial stiffness is the compliance of the large elastic arteries. Typically measured through ultrasound on the common carotid artery, arterial compliance represents the ability of an artery to expand and recoil due to changes in pressure. An artery that is able to expand under lower pressure is considered more compliant and less stiff [116].

Recurring studies have validated the ability of central arterial stiffness to predict the risk of future fatal cardiovascular events and total mortality [126]. In a population of more than 1,000 hypertensive individuals without CVD, the predictive value of central arterial stiffness on cardiovascular events was determined. Results showed that central arterial stiffness, measured by carotid-femoral PWV, was highly predictive of cardiovascular events, even after adjusting for traditional cardiovascular risk factors [127]. The predictive ability of PWV has been supported by a meta-analysis that included 17 longitudinal studies totaling more than 15,000 individuals with a 7-year average follow up. Results indicated a two-fold increase in cardiovascular events and mortality, as well as all-cause mortality for persons with higher aortic PWV compared to those with low aortic PWV [128]. The overall consensus is that the stiffness of large elastic arteries that occurs with age increases the risk of CVD and that measurements of central arterial stiffness allow us to determine which individuals are in need of intervention to reduce their risks.

Increases in central arterial stiffness reflect changes not only in the physical or structural properties of the arteries that occur with age but also in the functional elements of these arteries. Arteries are lined with single layer of cells called endothelial cells that release vasoactive substances (e.g., nitric oxide) that increase the diameter of an artery [129]. These cells comprise the inner most layer of the artery, called the endothelium, and maintaining a normally functioning endothelium is of paramount importance in reducing the future risk of CVD [129]. One way in which endothelial function can be determined is by measuring the relative increase in diameter to an increase in flow and shear stress

through the artery (flow-mediated dilation; FMD). FMD, measured through ultrasound of the brachial artery, is a validated marker of endothelium-dependent vasodilation and has been shown to be a string and independent predictor of future cardiovascular events [130, 131]. Regular aerobic exercise has been shown to improve FMD [130]. The improvements in FMD that occur through chronic exercise may be a means by which exercise reduces the risk of future CVD and premature death.

Osteoarthritis and Inflammation

Several lines of evidence confirm that low-grade inflammation contributes to the pathophysiology of OA [69, 132-134]. Synovial inflammation tends to act as a trigger for many symptoms of osteoarthritis, including joint pain, swelling, and stiffness [69, 92]. An observational study indicated that inflammation plays an important role in mediating arthritic joint inflammation and cartilage degradation [132]. Proinflammatory cytokines (e.g., IL-6, TNF-α and CRP) are elevated in OA patients [69, 133]. Elevated levels of TNF-α and CRP play a key role in increasing radiographic progression of arthritic knees [133, 134]. Furthermore, several studies have found a correlation between higher serum cytokine levels and both OA severity (pain) and reduced physical function [135, 136]. This set of circumstances accounts for the belief that factors and variables including pain, stiffness severity, and immobility, can undergo at least partial mediations in OA patients by measuring and regulating the level of chronic inflammation.

Role of Inflammation in Arterial Stiffness

Inflammation is not confined only to aggravating OA. A growing body of evidence indicates that inflammation may play a role in the pathogenesis of arterial stiffness and impairment of vascular function [137, 138]. Cross-sectional data suggest that central arterial stiffness and pulse pressure are significantly greater in patients with systemic lupus compared with age-matched healthy controls, which may be attributed to the elevated inflammatory state that accompanies lupus [139]. Moreover, endothelial function, measured by brachial FMD, is decreased in individuals with rheumatoid arthritis [140-142]. This raises the possibility that systemic inflammation and vascular dysfunction could be associated in the pathogenesis vascular remodeling in OA patients.

Osteoarthritis Management

Arthritis takes the form of a progressive degenerative joint disease whose prevalence increases markedly with advancing age. Lacking a medical cure for OA, a primary focus of the current therapeutic approach is aimed at pain relief through the administration of pain relieving medications that have a negligible functional benefit [6, 143]. Medications used to treat OA can be divided into two groups: 1) non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids that relieve the symptoms of OA and reduce inflammation and 2) disease-modifying anti-rheumatic drugs and biologic agents that may modify the disease and/or result in remission of its progression. Commonly, a physician may prescribe two or more such drugs, from both groups, in a regimen to control pain. While these medications might reduce pain, they do not slow the

progression of OA and are associated with harmful side effects [6, 144]. Administration of these medications drastically increases the incidence of cardiovascular events, leads to unfavorable side effects affecting the gastrointestinal and immune system, and fail to slow or arrest the progression of OA [6, 144].

Non-pharmacological interventions aim to provide support for patients coping with the consequences of OA, to play an active role in OA management, and to relieve its symptoms and slow or prevent joint damage [7]. Older studies in this area have become outdated or outmoded, as identification of OA patient characteristics have changed in the recent decade. Additionally, a substantial number of these older studies have proven flawed, due to methodological flaws and/or poor descriptions. Also, a knowledge gap has emerged regarding the implementation of effective non-pharmacological interventions in daily practice.

Effect of Physical Activity

Regular physical activity offers a multitude of health benefits for the general population, but especially provides specific and highly desirable therapeutic effects for patients with chronic diseases [145-147]. Moreover, physical activity reduces CVD risk profile, likely through improvements in vascular function in general and central arterial compliance in particular [8, 74]. The American College of Sports Medicine has published a set of guidelines for older adults and adults with clinically significant chronic conditions [9]. These guidelines suggest that every adult over 50 years old should undertake at least 30 minutes of moderate intensity physical activity most days of the

week to achieve optimal health benefits. If that level of physical activity cannot be achieved, a minimum of 20 minutes three days a week is believed to be the minimum physical activity to provide health benefits while compensating or accounting for the individual's aerobic fitness levels [9]. Furthermore, regular aerobic exercise could reduce inflammation cytokines levels [72]. Therapists and researchers must consider the predominant symptoms of OA, among them joint pain, stiffness, and fatigue, serve to impose some significant impediments for OA patients in regards to performing aerobic exercise [10].

Although exercise therapy is advised as the first-choice and preferred conventional management for OA, individuals who have OA are currently not adhering to the public health physical activity guideline recommendations [50].

Osteoarthritis and Exercise

Joint pain, stiffness, and decrease range of motion, common symptoms of osteoarthritis, can all result in diminished aerobic capacity, functional limitations, and lowered participation in social activities [148]. Ironically, this resultant decline in physical activity often exacerbates joint pain and intensifies joint stiffness [149].

Several methodical reviews of randomized controlled trials (RCTs) indicate that exercise therapy actually decreases pain as well as patient-reported disability in patients who have OA. Up to now however, the optimal exercise treatment is yet to be known [150, 151]. The results of exercise programs in medical trials are often not consistent, primarily due to the variability between programs (i.e. type, duration, intensity, and

frequency). In addition, included patients demographics vary with regard to radiographic severity of OA, sex, degree of mal-alignment, body mass index (BMI), and age [151].

Aerobic exercise, for instance cycling or walking, is commonly preferred and successful in managing lower limb OA. Aerobic exercise is an effective non-pharmacologic treatment with medium effect sizes for improvements in both function and pain [152]. With regard to the effect of weight-bearing activity in OA patients, some researchers have reported that weight-bearing exercise in the standing position, for instance walking, may exacerbate symptoms like inflammation, swelling, and pain if the knee joint becomes overloaded [17, 18].

Although strengthening exercise is advised, there is limited evidence linking any specific strengthening program to considerable benefits. Indeed, the same benefits have been found with isometric (without movement); isotonic (through range) [153]; and isokinetic strengthening exercise and with strengthening exercise carried out in non-weight bearing or weight-bearing positions [154, 155]. Furthermore, strengthening programs designed for knee OA have concentrated largely on quadriceps muscles or comprised strengthening of other lower limb muscles over and above the quadriceps. A methodical review showed small effect sizes for quadriceps strengthening for physical function and pain. On the contrary, moderate effect sizes were found for muscle strengthening that comprised a number of muscles in the lower limb.

Aquatic exercise seems to have similar effects on pain compared to land-based exercise in individuals with OA [156]. It is an alternative for patients with OA and it could be of use especially in those obese/overweight patients, and/or those with severe

joint-related symptoms. The water's buoyancy can help to improve the range of motion and pain with decreased loading to the joints. In addition, aquatic exercise may help improve aerobic capacity if it patients work at no less than 50 percent of their heart rate reserve.

A meta-analysis that comprised 48 RCTs with over 4,000 patients demonstrated that therapy programs that focus on a single exercise just are more effective in decreasing pain as well as patient-reported disability compared to those that combined different types of exercises with dissimilar goals in the same session [157]. It is worth mentioning that to attain optimal results, the program should be supervised, performed three times per week, and consist of no less than 12 sessions.

Recent studies indicate that physical activity has a potential role in lowering systemic inflammatory markers and alleviating disease-specific symptoms as well as fatigue levels in patients with arthritis [72]. Other studies indicate that exercise training may be the best option to prevent and recover the declines in physical function caused by OA [40, 90, 145-147]. However, the majority of recent studies in this area have focused on the effects of improving OA-related disease outcomes alone. Perceptive researchers recognize the need for more extensive research into the role of regular exercise on secondary outcomes such as vascular function and cardiovascular disease risk in OA patients.

Osteoarthritis and Regular Swimming Exercise

Non-pharmacologic rheumatology research has focused on the effects of dynamic

exercise on function in OA patients [145-147]. The initial focus was placed on determining appropriate doses or exercise regimen, and assessing safety and impact on joint integrity, and relief of pain and stiffening. More recent research has focused on the effect of exercise training on functional ability and other OA related outcomes [145-147]. Far less research has been conducted in determining the optimum modes of physical activity for adults with OA and the effectiveness of a low-impact aerobic activity such as cycling and swimming [158]. Although public health organizations universally agree that specific cardiovascular benefits arise from an active lifestyle for people suffering from OA, most land-based modes of exercise (e.g., walking, jogging, circuit training) are too difficult to perform in this population due to pain that is associated with the weight-bearing activities [148]. In fact, the amount of physical activity drops substantially across OA patient [148], and patients with arthritis are 33% to 55% weaker than age-matched healthy controls [159].

Recognizing that OA patients exhibit markedly increased mortality risk from cardiovascular events, increasing numbers of studies have been conducted to examine the association between OA and CVD. It has been emphasized that a more comprehensive and more widely encompassing regimen of research rather than the single component of physical activity will provide the most valuable outcomes [160, 161]. A number of epidemiological studies indicate a lower incidence of cardiovascular disease in more physically active OA patients. The greater the physical activity, the lower the risk of cardiovascular dysfunction or mortality [162, 163]. In this context, swimming might be the ideal form of exercise for people with OA.

Swimming forms one of the most comprehensively beneficial forms of exercise, since it offers three very obvious advantages: easily accessible, inexpensive, and isotonic. The most obvious advantage of swimming for arthritis patient is the buoyancy of water, which relieves the patient of the need to lift any weight or stress placed by one's own body weight and bulk. Unlike weight lifting that operates against any resistance and muscle straining, swimming does not involve compressive joint forces [164]. Thus, swimming offers one of the lowest risk exercises that could avoid musculoskeletal injuries that frequently occur in OA patients [165]. The incidence of accidents among swimmers ranks far below that of runners or bicyclists [165]. Moreover, the dual advantages of cooler water temperatures and increased thermoconductivity of water lowers the risks of heat-related illness or trauma such as heat stroke or heat exhaustion [166]. Obviously, swimming emerges as an ideal exercise for elderly and/or OA patients. Most importantly, swimming has been recommended for health promotion and prevention and treatment of risk factors for cardiovascular disease [167]. Recent controlled study from our laboratory showed that swimming training significantly decreased systolic blood pressure and improved vascular function, in particular endothelial function [77]. Swimming ranks second only to walking as the most widely popular form of exercise for persons of all ages and health conditions [168]. The American College of Rheumatology recommends swimming for individuals with OA. However, there is no evidence that swimming provides any benefits to this population [7].

Physiologically speaking, the claim that the benefits which are generated from cycling and walking also come from swimming is unsubstantiated. In fact, swimming is a unique type of exercise in many aspects including position, muscle group used, and medium. Swimming is mostly an upper body exercise and also, it is performed in a supine position in water as compared to cycling or walking on land. Nevertheless, the act of exercising in water exposes a person to several hemodynamic experiences which are quite different to experience when exercising on land. Such experiences include the relocation of blood volume to the central arteries, the diving reflex, and pressure response [12, 169]. Despite these benefits from swimming, medical research indicates that swimming regularly actually may not be as beneficial as most people think it is. When swimmers are compared to other athletes in endurance sports, research outcomes indicate that swimmers typically have high levels of blood pressure [170-172]. Furthermore, when swimming is compared to walking or jogging, swimmers tend to experience a higher average arterial blood pressure when functioning at a similar heart rate level [173]. In one of the latest intervention studies, has been shown that swimming may bring harmful, rather than beneficial effects [174]. The study employed elder women with normal blood pressure levels were randomly assigned into either a 6-month swimming or walking training program [174]. The outcomes indicated that the women actually benefited more from the walking and jogging compared to the swimming program. In fact, the researchers identified considerable increases in diastolic and systolic blood pressure in the swimming program which was contrary to the findings of the walking and jogging program which found no changes in blood pressure [174].

Chapter 5: Summary and Future Directions

Summary

Osteoarthritis is the most common form of arthritis and is the leading cause of disability in older adults [14]. Moreover, patients with OA are at higher risk of cardiovascular disease (CVD) [2, 14, 63-67]. Because no cure is currently available for osteoarthritis, the treatment plan has focused on reducing pain and improving function while minimizing adverse effects. Although the American College of Rheumatology has recommended that aerobic exercise in the general osteoarthritis treatment plans [7], the associated joint pain and stiffness act as a significant barrier for those attempting to perform land-based weight-bearing activity [10]. For this reason, swimming appears to be the ideal form of aerobic exercise for middle-aged and older patients with osteoarthritis. The minimal weight-bearing stress facilitated by the buoyancy effects of water is an important element for patients afflicted with osteoarthritis that exhibit orthopedic problems affecting the hips and knees. Surprisingly, however, no study has been conducted to investigate the effects of swimming exercise training in patients with osteoarthritis.

The primary purpose of these dissertation studies was to investigate the effects of swimming exercise compared to stationary cycling on functional capacity, pain, vascular function, and inflammation in middle-aged and older adults with OA. We hypothesized

that both swimming exercise and cycling exercise would result in similar improved vascular function, physical function, and quality of life, and reduced pain and inflammation in middle-aged and older adults with osteoarthritis. We used a controlled, randomized interventional study approach, in which forty-eight sedentary middle-aged and older adults with OA underwent either swimming or cycling interventions. Supervised exercise training was performed for 45 minutes 3 days/week at 60-70% heart rate reserve for 12 weeks.

The primary findings from the present study were as follows: body mass, visceral adiposity, and waist and hip circumference were significantly decreased in both exercise training groups. There were reductions in pain and stiffness accompanied by increased reported physical function, as determined by the WOMAC index, in both exercise groups. Participants in both exercise training groups demonstrated significant increases in distance covered during the 6-min walk test. Maximal grip strength and isokinetic knee extensor and flexor strength significantly increased in both swimming and cycling exercise training groups. Moreover, significant reductions in central arterial stiffness following both exercise interventions, and the arterial destiffening effects were observed all across various measures of arterial stiffness. Central systolic BP and pulse pressure decreased significantly with both exercise interventions whereas peripheral (brachial) BP did not change. An improvement in endothelium-dependent vasodilation was observed after the swimming, but not after the cycling intervention. Both exercise training decreased levels of inflammation, as indicated by reductions in plasma concentrations of the inflammatory cytokine IL-6.

There were several limitations of the present study. Participants only performed supervised exercise for 3 months. Although we observed health benefits of exercise training in this time span, it is unknown if continued participation in exercise training would maintain these benefits. An additional limitation is the lack of participant blinding to treatment allocation. Swimming is considered an ideal form of exercise for patients with osteoarthritis. Placement in the alternate exercise condition may have affected self-reported outcomes or motivation. This is unlikely as they number of drop-outs were equal between exercise interventions. Lastly, we only included patients with mild-to-moderate radiographic OA. Not included were patients with advance stage of OA that were using a walker or were awaiting a joint replacement. Therefor, we cannot generalize the present findings to that population.

Taken together, these findings indicate that 3 months of non-weight bearing exercise training, are similar in improving general physical function, muscular strength, pain, and joint stiffness, as well as vascular function in patients with osteoarthritis. While both exercise interventions were successful in decreasing central arterial stiffness, only swimming exercise was able to improve vascular endothelial function. These findings are of paramount clinical importance to patients with OA, as swimming is a desirable mode of exercise, but is often viewed as inferior to land-based exercise in regards to maximizing health benefits gained from exercise.

Future Directions

Traditionally, participating in an exercise training program, such as walking, jogging, or resistance training, has been used to reduce risk factors associated with cardiovascular disease (CVD). While these types of exercise are effective in reducing risk of CVD, these modalities of exercise may not be possible in all individuals, specifically those who have disease that limits their ability to participate in weight bearing activity, such as OA. In fact, participating in land-based weight bearing activity may be a detriment to patients with OA, exacerbating joint pain and stiffness, which could accelerate its disease progression.

For decades, swimming has grown in popularity, being praised by health and fitness experts as an exercise modality to improve cardiovascular fitness [9, 76, 175-177]. Second to walking, swimming is the most liked recreational activity in the United States [168]**.** A major appeal of swimming may be due to the reduced chance of injuries because it is minimally weight bearing [12, 165]. For these reasons, swimming may be an excellent exercise training modality for patients with OA, as well as any other disease population with limited mobility or exercise tolerance [178]. However, the importance of daily swimming in promoting health may not be as widely known, as its positive impacts on preventing fitness related diseases are relatively unknown [164]. While there is no question regarding the popularity of swimming as a recreational activity [168, 179], there are limited data to support the efficacy of daily swimming to reduce the risk of CVD.

In the present study we observed improvements in function, inflammation, pain,

and vascular outcomes following 12 weeks of swimming exercise in patients with OA. Clearly, the benefits of regular exercise for patients with OA extend to swimming. Thus, future studies to investigate the efficacy of daily swimming on improvements in vascular function in large arteries of other types of arthritis, such as rheumatoid arthritis. Presently, no studies have investigated the benefits of swimming in patients with rheumatoid arthritis (RA). RA is an auto-immune disease that targets the joints, but is also characterized by high inflammation. Based on the findings of the present studies in which 12-weeks of swimming exercise not only improved symptoms of OA, but also reduced inflammation, it is possible that swimming exercise may be an excellent form of exercise for patients with RA.

Appendix A: Abbreviations and Definition

Arterial distensibility = Relative diameter (or area) change for a pressure increment; the inverse of elastic modulus

Arterial compliance = Absolute diameter (or area) change for a given pressure step at fixed vessel length

ANOVA = analysis of variance

BP = blood pressure

BMI = Body mass index

cfPWV = carotid-femoral pulse wave velocity

CVD = cardiovascular disease

FMD = flow-mediated dilation

HbA1c = glycated hemoglobin

MI = myocardial infarction

NO = nitric oxide

Sedentary = description of an individual who has participated in less than 1 hour a week of physical activity for one year prior to this study.

Middle-aged and older adults = age between 40-90 years

β-stiffness = a measure of arterial stiffness independent of the blood pressure effect

Vascular function = general term to describe changes in the arterial tree including arterial stiffness and endothelial-dependent vasodilation

IFN = Interferon

TNF = Tumor necrosis factors

WOMAC = Western Ontario and McMaster University Osteoarthritis Index

Appendix B: Health Research Questionnaire

Health Research Questionnaire

Cardiovascular Aging Research Laboratory
University of Texas at Austin

Personal Information

Today's Date _____ Please print your name _____
Phone Number _____ Email _____
Date of Birth _____ Age _____ Sex ☐ Male ☐ Female
Who is your physician? _____ Phone _____
In case of emergency, contact _____ Phone _____

Please circle the highest grade in school you have completed:

Elementary school	1	2	3	4	5	6	7	8
High school	9	10	11	12				
College/Post Grad	13	14	15	16	17	18	19	20+

What is your martial status? ☐ Single ☐ Married; ☐ Widowed ☐ Divorced; Separated
Ethnic Background: ☐ Hispanic or Latino ☐ Not Hispanic or Latino
Race:
☐ White ☐ American Indian/Alaskan Native ☐ Pacific Islander
☐ Black or African American ☐ Asian

Symptoms or Signs Suggestive of Disease

Check appropriate box:

Yes	No		
☐	☐	1.	Have you experienced unusual pain or discomfort in your cheek, neck, jaw, arms or other areas that may be due to heart problems?
☐	☐	2.	Have you experienced unusual fatigue or shortness of breath at rest, during usual activities, or during mild-to-moderate exercise (e.g., climbing stairs, carrying groceries, brisk walking, cycling)?
☐	☐	3.	When you stand up, or sometimes during the night while you are sleeping, do you have difficulty breathing?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you suffer from swelling of the ankles (ankle edema)?
☐	☐	6.	Have you experienced an unusual and rapid throbbing or fluttering of the heart?
☐	☐	7.	Have you experienced severe pain in your leg muscles during walking?
☐	☐	8.	Has a doctor told you that you have a heart murmur?

Chronic Disease Risk Factors

Check appropriate box:

Yes	No		
☐	☐	9a.	Are you a male over age 45 years or a female over age 55 years?
☐	☐		b. Are you a female who has experienced premature menopause?
☐	☐		c. If you answered "yes" to 9b, are you on estrogen replacement therapy?
☐	☐	10.	Has your father or brother had a heart attack or died suddenly of heart disease before the age of 55; has your mother or sister experienced these heart problems before the age of 65?

Yes	No		
☐	☐	11.	Are you a current cigarette smoker?
☐	☐	12.	Has a doctor told you that you have high blood pressure (more than 140/90 mm Hg) or a heart condition?
☐	☐	13.	Is your total serum cholesterol greater than 200 mg/dl, or has a doctor told you that your cholesterol is at a high risk-level?
☐	☐	14.	Do you have diabetes mellitus?
☐	☐	15.	Are you physically inactive and sedentary (little physical activity on the job or during leisure time)?
☐	☐	16.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	17.	During the past year, would you say that you have experienced enough stress, strain, and pressure to have a significant effect on your health?
☐	☐	18.	Do you eat foods nearly every day that are high in fat and cholesterol such as fatty meats, cheese, fried foods, butter, whole milk, or eggs?
☐	☐	19.	Do you weigh 30 or more pounds than you should?
☐	☐	20.	Do you know of any other reason you should not do physical activity?

Medical History

21. *Please check which of the following conditions you have had or now have. Also check medical conditions in your family (father, mother, brother(s), or sister(s)). Check as many as apply.*

Self	Family	Medical Condition	Self	Family	Medical Condition
☐	☐	Coronary heart disease, heart attack; by-pass surgery	☐	☐	Major injury/fracture to foot, leg, knee
☐	☐	Arrhythmias	☐	☐	Major injury to back or neck
☐	☐	Angina	☐	☐	Major injury/fracture to hip or shoulder
☐	☐	High blood pressure	☐	☐	Rheumatoid Arthritis
☐	☐	Peripheral vascular disease	☐	☐	Osteoarthritis
☐	☐	Phlebitis or emboli	☐	☐	Gout
☐	☐	Other heart problems	☐	☐	Osteoporosis
☐	☐	Stroke	☐	☐	Fibromyalgia
☐	☐	Asthma	☐	☐	Diabetes mellitus
☐	☐	Bronchitis	☐	☐	Kidney disease
☐	☐	COPD (emphysema)	☐	☐	Cataracts
☐	☐	Lung cancer	☐	☐	Glaucoma
☐	☐	Breast cancer	☐	☐	Hearing loss
☐	☐	Prostate cancer	☐	☐	Depression
☐	☐	Skin cancer	☐	☐	Anxiety, phobias
☐	☐	Colorectal cancer	☐	☐	Eating disorders
☐	☐	Other cancer. Specify:	☐	☐	Sleeping problems
☐	☐	Gallstones/gallbladder disease	☐	☐	Substance abuse problems (alcohol, other drugs, etc.)
☐	☐	Liver disease (cirrhosis)	☐	☐	Chronic Fatigue Syndrome
☐	☐	Hepatitis	☐	☐	Thyroid problems

Self	Family	Medical Condition	Self	Family	Medical Condition
☐	☐	Anemia (low iron)	☐	☐	Hysterectomy
☐	☐	Stomach/duodenal ulcer	☐	☐	Problems with menstruation
☐	☐	Rectal growth or bleeding	☐	☐	Post-menopausal (date:)
☐	☐	Crohne's disease	☐	☐	Raynaud's disease
☐	☐	Irritable bowel syndrome	☐	☐	Allergies
☐	☐	Marfan's syndrome			

Any other health problems. Please specify and include information on any recent illnesses, hospitalizations, or surgical procedures.

22. *Please check any of the following medications you take regularly and give the name of the medication.*

Medication	Name of Medication
☐ Heart medicine	_____
☐ Blood pressure medicine	_____
☐ Blood cholesterol medicine	_____
☐ Hormones	_____
☐ Birth control medicine	_____
☐ Medicine for breathing/lungs	_____
☐ Insulin	_____
☐ Other medicine for diabetes	_____
☐ Arthritis medicine	_____
☐ Medicine for depression	_____
☐ Medicine for anxiety	_____
☐ Thyroid medicine	_____
☐ Medicine for ulcers	_____
☐ Painkiller medicine	_____
☐ Allergy medicine	_____
☐ Other (please specify)	_____
☐ Do you have any drug allergies?	_____
☐ Dietary supplements (please specify)	_____

Body Weight

23. What is the most you have ever weighed? _____ pounds

24. Are you now trying to:

☐ Lose weight ☐ Gain weight ☐ Stay about the same ☐ Not trying to do anything

Stress

25. During the past month, how would you rate your overall level of stress?

☐ Very high ☐ High ☐ Moderate ☐ Low

26. In the past year, how much effect has stress had on your health?

☐ A lot ☐ Some ☐ Hardly any or none

27. On average, how many hours of sleep do you get in a 24-hour period?

☐ Less than 5 ☐ 5-6.9 ☐ 7-9 ☐ More than 9

Substance Use

28. How would you describe your cigarette smoking habits?

☐ Never smoked

☐ Used to smoke. How many years has it been since you smoked? _____ years

☐ Still smoke. How many cigarettes a day do you smoke on average? ___cigarettes/day

29. How many alcoholic drinks do you consume? (A "drink" is a glass of wine, a wine cooler, a 16oz bottle/12oz can of beer, a shot glass of liquor, or a mixed drink).

☐ Never use alcohol ☐ Less than 1 per week ☐ 1-6 per week ☐ 1 per day
☐ 2-3 per day ☐ More than 3 per day

30. In one sitting, how many drinks do you typically consume? _____

31. How many cups (8 ounces) of coffee do you drink per day? _____

32. How many ounces of sodas containing caffeine do you drink per day? _____

Physical Fitness, Physical Activity/Exercise

33. Considering a **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your **free time** (write on each line the appropriate number).

	Times Per Week
a) **STRENUOUS EXERCISE (HEART BEATS RAPIDLY)** (i.e. running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) **MODERATE EXERCISE (NOT EXHAUSTING)** (i.e. fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) **MILD EXERCISE (MINIMAL EFFORT)** (i.e. yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

34. Considering a 7-Day period (a week), during your leisure-time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)

☐ OFTEN ☐ SOMETIMES ☐ NEVER/RARELY

35. How long have you exercised or played sports regularly?

☐ I do not exercise regularly ☐ Less than 1 year ☐ 1-2 years
☐ 2-5 years ☐ 5-10 years ☐ More than 10 years

Occupational Health

36. Please describe your main job title and duties.

_____

37. How much hard physical work is required on your job?

☐ A great deal ☐ A moderate amount ☐ A little ☐ None

Reproductive Health

38. What is the date of your last menstrual cycle?

_____

X-ray testing

39. Have you recently had or are you planning to have barium tests or a nuclear medicine scan or injection with an x-ray dye?

☐ No ☐ Yes If yes, when? _____

Appendix C: The Western Ontario and McMaster University Oseoarthitis Index (WOMAC)

Name:_____ Date:_____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Appendix D: SF-36Questionnaire

SF-36 QUESTIONNAIRE

(1992 -- Medical Outcomes Trust)

Subject Name: _____ **Date:** _____

1. In general, would you say your health is: (circle one)

   Excellent Very good Good Fair Poor

2. Compared to one year ago, how would you rate your health in general now? (circle one)

   Much better now than one year ago.

   Somewhat better now than one year ago.

   About the same as one year ago.

   Somewhat worse than one year ago.

   Much worse than one year ago.

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Mark each answer with an **X**)

ACTIVITIES	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited At All**
a. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports			
b. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing **several** flights of stairs			
e. Climbing **one** flight of stairs			
f. Bending, kneeling or stooping			
g. Walking **more than a mile**			
h. Walking **several blocks**			
i. Walking **one block**			
j. Bathing or dressing yourself			

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Mark each answer with an **X**)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activites		
b. **Accomplished less** than you would like		
c. Were limited in the **kind** of work or other activities		
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Mark each answer with an **X**)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities		
b. **Accomplished less** than you would like		
c. Didn't do work or other activities as **carefully** as usual		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (circle one)

Not at all Slightly Moderately Quite a bit Extremely

7. How much bodily pain have you had during the past 4 weeks? (circle one)

None Very mild Mild Moderate Severe Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks – (Mark each answer with an **X**)

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Did you feel full of pep?						
b. Have you been a very nervous person?						
c. Have you felt so down in the dumps that nothing could cheer you up?						
d. Have you felt calm and peaceful?						
e. Did you have a lot of energy?						
f. Have you felt downhearted and blue?						
g. Did you feel worn out?						
h. Have you been a happy person?						
i. Did you feel tired?						

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (circle one)

All of the time Most of the time Some of the time A little of the time None of the time

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people					
b. I am as healthy as anybody I know					
c. I expect my health to get worse					
d. My health is excellent					

Appendix E: Seven-Day Medication Survey form

☐ *Pre* ☐ *Post*

Subject ID:_____ **Date:_____**

Please record all prescription and over-the-counter medications for arthritis you take each day such as aspirin, Tylenol, Advil, Motrin, or Nuprin. Including cold and allergy medication, vitamins, herbal remedies, and other supplements.

Carefully copy the MEDICATION NAME. Using periods to indicate decimal points, copy the formulation STRENGTH (weight for solids and *concentration* for non-solids). Using upper case letters and standard abbreviations, copy the UNITS used to measure strength.

It is best if you can complete this information at the end of each day so you don't forget to record any tablets you have taken.

Date **MON/DD/YYYY**	**Medication name**	**Strength/Units**	**Number of tables**
	1)		
	2)		
	3)		
	4)		
	5)		
	1)		
	2)		
	3)		
	4)		
	5)		

Appendix F: Three-Day Dietary Record

3-Day Food Intake Record Instructions

1. Record day of the week and date for everything you eat and drink for three days (two week days & one weekend day) prior to arriving at your appointment.
2. Include the time, amount and type of food/beverage consumed. Provide as much detail as possible, including brand names when available. For example, instead of recording "cereal with milk", record "1.5 cups Kashi GoLean cereal with 6 oz low-fat milk". Instead of "1 slice wheat toast with jam", record "1 slice Orowheat 100% whole-wheat toast with 1tsp Smucker's low-sugar strawberry preserves". See sample food log for more examples.
3. For combination foods such as chili, soup, casseroles, sandwiches, list all items in the food and amounts of each item.
4. For dairy products (milk, cheese, yogurt, etc) record whether, regular (whole), lowfat (1%), reduced fat (2%), or nonfat (skim).
5. Include sweeteners (sugar, honey, syrup, etc) and fats (cream, half&half, milk, etc) added to coffee, tea, etc; as well as spreads on breads and dressings on salads.
6. For meats, indicate type (ground, sirloin, etc) and % lean, if known.
7. Continue eating your normal diet during the recording days before your first testing session. After your first testing session, we will give you a copy of your food records and ask you to duplicate this diet the 3 days before your second testing session. Please continue to record your food on the 3 days before your second testing session.

-See reverse for sample food log-

Sample 3 Day Food Intake	Day of Week:		Date:
Time	*Amount*	*Brand*	*Food/Beverage*
8am	8 oz		Nonfat milk (in cereal)
	12 oz		Black coffee
	1 Tsp		Sugar in coffee
	1.5 Cups	Nature's Path	Heritage Heirloom Whole Grains Cereal
	1 T	Sun-Maid	Fruit bits
	1 medium		Cara Cara navel orange
12pm	1.3 Cups	Homemade	Chili: ½ Cup 70% lean ground beef, 1 T onion, 2 T garbanzo beans, 2T black beans, 2 T red sweet pepper
	3 T		Grated cheddar/jack cheese, regular
	½ Cup		Fresh strawberries
	½ Cup	Stoneyfield	Lowfat vanilla yogurt
	2 T		Raw almonds
3pm	1	Cliff	Chocolate Builder's Bar
6pm	5 oz		Grilled chicken breast, skinless
	¾ Cup		Slaw: ¼ cup cabbage, ¼ grated carrots, ¼ broccoli, 1 tsp olive oil, 1 tsp cider vinegar
	1 piece	Kirkland Signature	Multigrain bread
	2 tsp		honey
	½ tsp		butter
	¾ Cup		Grilled vegetables: ¼ cup yellow squash, ¼ red pepper, ¼ cup eggplant

Day ___

3 Day Food Intake	Day of Week:	Date:	
Time	***Amount***	***Brand***	***Food / Beverage***

References

1. Centers for Disease, C. and Prevention, *Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation --- United States, 2007-2009.* MMWR Morb Mortal Wkly Rep, 2010. **59**(39): p. 1261-5.

2. Haara, M.M., et al., *Osteoarthritis of finger joints in Finns aged 30 or over: prevalence, determinants, and association with mortality.* Ann Rheum Dis, 2003. **62**(2): p. 151-8.

3. Helmick, C.G., et al., *Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I.* Arthritis Rheum, 2008. **58**(1): p. 15-25.

4. Lawrence, R.C., et al., *Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II.* Arthritis Rheum, 2008. **58**(1): p. 26-35.

5. Hootman, J.M. and C.G. Helmick, *Projections of US prevalence of arthritis and associated activity limitations.* Arthritis Rheum, 2006. **54**(1): p. 226-9.

6. Cannon, C.P., et al., *Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison.* Lancet, 2006. **368**(9549): p. 1771-81.

7. Hochberg, M.C., et al., *American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies*

in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken), 2012. **64**(4): p. 465-74.

8. Tanaka, H. and M.E. Safar, *Influence of lifestyle modification on arterial stiffness and wave reflections.* Am J Hypertens, 2005. **18**(1): p. 137-44.

9. Pescatello, L.S., et al., *American College of Sports Medicine position stand. Exercise and hypertension.* Med Sci Sports Exerc, 2004. **36**(3): p. 533-53.

10. Hedbom, E. and H.J. Hauselmann, *Molecular aspects of pathogenesis in osteoarthritis: the role of inflammation.* Cell Mol Life Sci, 2002. **59**(1): p. 45-53.

11. Tanaka, H., et al., *Dry-land resistance training for competitive swimming.* Med Sci Sports Exerc, 1993. **25**(8): p. 952-9.

12. Becker, B. and A. Cole, *Aquatic rehabilitation.* Rehabilitation medicine: principles and practice, 3rd ed. Philadelphia: Lippincott–Raven, 1998: p. 897-901.

13. Sheldahl, L.M., et al., *Effects of exercise in cool water on body weight loss.* Int J Obes, 1982. **6**(1): p. 29-42.

14. Centers for Disease, C. and Prevention, *Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation--United States, 2010-2012.* MMWR Morb Mortal Wkly Rep, 2013. **62**(44): p. 869-73.

15. Lievense, A.M., et al., *Influence of sporting activities on the development of osteoarthritis of the hip: a systematic review.* Arthritis Rheum, 2003. **49**(2): p. 228-36.

16. Vignon, E., et al., *Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS).* Joint Bone Spine, 2006. **73**(4): p. 442-55.

17. Baliunas, A.J., et al., *Increased knee joint loads during walking are present in subjects with knee osteoarthritis.* Osteoarthritis Cartilage, 2002. **10**(7): p. 573-9.

18. Lucchinetti, E., et al., *Cartilage viability after repetitive loading: a preliminary report.* Osteoarthritis Cartilage, 2002. **10**(1): p. 71-81.

19. Salacinski, A.J., et al., *The effects of group cycling on gait and pain-related disability in individuals with mild-to-moderate knee osteoarthritis: a randomized controlled trial.* J Orthop Sports Phys Ther, 2012. **42**(12): p. 985-95.

20. Mangione, K.K., et al., *The effects of high-intensity and low-intensity cycle ergometry in older adults with knee osteoarthritis.* J Gerontol A Biol Sci Med Sci, 1999. **54**(4): p. M184-90.

21. Roddy, E., et al., *Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee--the MOVE consensus.* Rheumatology (Oxford), 2005. **44**(1): p. 67-73.

22. Bennell, K., et al., *Exercise and osteoarthritis: cause and effects.* Compr Physiol, 2011. **1**(4): p. 1943-2008.

23. Kellgren, J.H. and J.S. Lawrence, *Radiological assessment of osteo-arthrosis.* Ann Rheum Dis, 1957. **16**(4): p. 494-502.

24. Sallis, J.F., et al., *Physical activity assessment methodology in the Five-City Project.* Am J Epidemiol, 1985. **121**(1): p. 91-106.

25. Medicine, A.C.o.S., *ACSM's guidelines for exercise testing and prescription*. 2013: Lippincott Williams & Wilkins.

26. Tanaka, H., K.D. Monahan, and D.R. Seals, *Age-predicted maximal heart rate revisited.* J Am Coll Cardiol, 2001. **37**(1): p. 153-6.

27. Tanaka, H., et al., *Influence of body fatness on the coronary risk profile of physically active postmenopausal women.* Metabolism, 1998. **47**(9): p. 1112-20.

28. Dinenno, F.A., et al., *Limb blood flow and vascular conductance are reduced with age in healthy humans: relation to elevations in sympathetic nerve activity and declines in oxygen demand.* Circulation, 1999. **100**(2): p. 164-70.

29. Enright, P.L., *The six-minute walk test.* Respir Care, 2003. **48**(8): p. 783-5.

30. Park, W., et al., *Effect of walking speed and placement position interactions in determining the accuracy of various newer pedometers.* Journal of Exercise Science & Fitness, 2014.

31. Barnes, J.N., et al., *Arterial stiffening following eccentric exercise-induced muscle damage.* J Appl Physiol (1985), 2010. **109**(4): p. 1102-8.

32. Mikesky, A.E., et al., *Effects of strength training on the incidence and progression of knee osteoarthritis.* Arthritis Rheum, 2006. **55**(5): p. 690-9.

33. Bellamy, N., et al., *Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee.* J Rheumatol, 1988. **15**(12): p. 1833-40.

34. Angst, F., A. Aeschlimann, and G. Stucki, *Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities.* Arthritis Rheum, 2001. **45**(4): p. 384-91.

35. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.

36. Altman, D.G., et al., *The revised CONSORT statement for reporting randomized trials: explanation and elaboration.* Ann Intern Med, 2001. **134**(8): p. 663-94.

37. White, I.R., J. Carpenter, and N.J. Horton, *Including all individuals is not enough: lessons for intention-to-treat analysis.* Clin Trials, 2012. **9**(4): p. 396-407.

38. Fernandes, L., et al., *EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis.* Ann Rheum Dis, 2013. **72**(7): p. 1125-35.

39. Conaghan, P.G., et al., *Care and management of osteoarthritis in adults: summary of NICE guidance.* BMJ, 2008. **336**(7642): p. 502-3.

40. Zhang, W., et al., *OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines.* Osteoarthritis Cartilage, 2008. **16**(2): p. 137-62.

41. Zhang, W., et al., *EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee*

for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis, 2007. **66**(3): p. 377-88.

42. Gill, S.D., H. McBurney, and D.L. Schulz, *Land-based versus pool-based exercise for people awaiting joint replacement surgery of the hip or knee: results of a randomized controlled trial.* Arch Phys Med Rehabil, 2009. **90**(3): p. 388-94.

43. Foley, A., et al., *Does hydrotherapy improve strength and physical function in patients with osteoarthritis--a randomised controlled trial comparing a gym based and a hydrotherapy based strengthening programme.* Ann Rheum Dis, 2003. **62**(12): p. 1162-7.

44. Silva, L.E., et al., *Hydrotherapy versus conventional land-based exercise for the management of patients with osteoarthritis of the knee: a randomized clinical trial.* Phys Ther, 2008. **88**(1): p. 12-21.

45. Green, J., et al., *Home exercises are as effective as outpatient hydrotherapy for osteoarthritis of the hip.* Br J Rheumatol, 1993. **32**(9): p. 812-5.

46. Becker, B.E. and A.J. Cole, *Swimming onward: the future of aquatic rehabilitation.* J Back Musculoskelet Rehabil, 1994. **4**(4): p. 319-20.

47. Ball, K., D. Crawford, and N. Owen, *Too fat to exercise? Obesity as a barrier to physical activity.* Aust N Z J Public Health, 2000. **24**(3): p. 331-3.

48. Lim, K. and L. Taylor, *Factors associated with physical activity among older people--a population-based study.* Prev Med, 2005. **40**(1): p. 33-40.

49. Centers for Disease, C. and Prevention, *Arthritis as a potential barrier to physical activity among adults with obesity--United States, 2007 and 2009.* MMWR Morb Mortal Wkly Rep, 2011. **60**(19): p. 614-8.

50. Dunlop, D.D., et al., *Objective physical activity measurement in the osteoarthritis initiative: Are guidelines being met?* Arthritis Rheum, 2011. **63**(11): p. 3372-82.

51. Theis, K.A., et al., *Prevalence and correlates of arthritis-attributable work limitation in the US population among persons ages 18-64: 2002 National Health Interview Survey Data.* Arthritis Rheum, 2007. **57**(3): p. 355-63.

52. Tanaka, H., *Effects of cross-training. Transfer of training effects on VO2max between cycling, running and swimming.* Sports Med, 1994. **18**(5): p. 330-9.

53. Tanaka, H., et al., *Aging, habitual exercise, and dynamic arterial compliance.* Circulation, 2000. **102**(11): p. 1270-5.

54. Chuter, V.H., et al., *The efficacy of a supervised and a home-based core strengthening programme in adults with poor core stability: a three-arm randomised controlled trial.* Br J Sports Med, 2014.

55. Gill, T.M., et al., *A program to prevent functional decline in physically frail, elderly persons who live at home.* N Engl J Med, 2002. **347**(14): p. 1068-74.

56. Littbrand, H., et al., *The effect of a high-intensity functional exercise program on activities of daily living: a randomized controlled trial in residential care facilities.* J Am Geriatr Soc, 2009. **57**(10): p. 1741-9.

57. Baker, K.R., et al., *The efficacy of home based progressive strength training in older adults with knee osteoarthritis: a randomized controlled trial.* J Rheumatol, 2001. **28**(7): p. 1655-65.

58. Fransen, M., et al., *Physical activity for osteoarthritis management: a randomized controlled clinical trial evaluating hydrotherapy or Tai Chi classes.* Arthritis Rheum, 2007. **57**(3): p. 407-14.

59. Huang, M.H., et al., *A comparison of various therapeutic exercises on the functional status of patients with knee osteoarthritis.* Semin Arthritis Rheum, 2003. **32**(6): p. 398-406.

60. Hughes, S.L., et al., *Impact of the fit and strong intervention on older adults with osteoarthritis.* Gerontologist, 2004. **44**(2): p. 217-28.

61. van Baar, M.E., et al., *Effectiveness of exercise in patients with osteoarthritis of hip or knee: nine months' follow up.* Ann Rheum Dis, 2001. **60**(12): p. 1123-30.

62. Belza, B., et al., *Does adherence make a difference? Results from a community-based aquatic exercise program.* Nurs Res, 2002. **51**(5): p. 285-91.

63. Philbin, E.F., et al., *Cardiovascular fitness and health in patients with end-stage osteoarthritis.* Arthritis Rheum, 1995. **38**(6): p. 799-805.

64. Ong, K.L., et al., *Arthritis: its prevalence, risk factors, and association with cardiovascular diseases in the United States, 1999 to 2008.* Ann Epidemiol, 2013. **23**(2): p. 80-6.

65. Cerhan, J.R., et al., *Decreased survival with increasing prevalence of full-body, radiographically defined osteoarthritis in women.* Am J Epidemiol, 1995. **141**(3): p. 225-34.

66. Nuesch, E., et al., *All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study.* BMJ, 2011. **342**: p. d1165.

67. Singh, G., et al., *Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey.* Am J Manag Care, 2002. **8**(15 Suppl): p. S383-91.

68. Barnes, J.N., et al., *Arterial stiffening, wave reflection, and inflammation in habitually exercising systemic lupus erythematosus patients.* Am J Hypertens, 2011. **24**(11): p. 1194-200.

69. Otterness, I.G., et al., *An analysis of 14 molecular markers for monitoring osteoarthritis: segregation of the markers into clusters and distinguishing osteoarthritis at baseline.* Osteoarthritis Cartilage, 2000. **8**(3): p. 180-5.

70. Saleh, A.S., et al., *Arterial stiffness and hand osteoarthritis: a novel relationship?* Osteoarthritis Cartilage, 2007. **15**(3): p. 357-61.

71. Koutroumpas, A., et al., *Erosive Hand Osteoarthritis is Associated with Subclinical Atherosclerosis and Endothelial Dysfunction.* Int J Biomed Sci, 2013. **9**(4): p. 217-23.

72. Cooney, J.K., et al., *Benefits of exercise in rheumatoid arthritis.* J Aging Res, 2011. **2011**: p. 681640.

73. Adamopoulos, S., et al., *Physical training reduces peripheral markers of inflammation in patients with chronic heart failure.* Eur Heart J, 2001. **22**(9): p. 791-7.

74. Helmick, C.G., et al., *Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I.* Arthritis & Rheumatism, 2008. **58**(1): p. 15-25.

75. Voelker, R., *Few adults with knee osteoarthritis meet national guidelines for physical activity.* JAMA, 2011. **306**(13): p. 1428, 1430.

76. *Physical exercise in the management of hypertension: a consensus statement by the World Hypertension League.* J Hypertens, 1991. **9**(3): p. 283-7.

77. Nualnim, N., et al., *Effects of swimming training on blood pressure and vascular function in adults >50 years of age.* Am J Cardiol, 2012. **109**(7): p. 1005-10.

78. Kingwell, B.A., et al., *Arterial compliance increases after moderate-intensity cycling.* Am J Physiol, 1997. **273**(5 Pt 2): p. H2186-91.

79. DeVan, A.E., et al., *Acute effects of resistance exercise on arterial compliance.* J Appl Physiol (1985), 2005. **98**(6): p. 2287-91.

80. Cortez-Cooper, M.Y., J.A. Supak, and H. Tanaka, *A new device for automatic measurements of arterial stiffness and ankle-brachial index.* Am J Cardiol, 2003. **91**(12): p. 1519-1522.

81. Sugawara, J., et al., *Age-associated elongation of the ascending aorta in adults.* JACC Cardiovasc Imaging, 2008. **1**(6): p. 739-48.

82. Dinenno, F.A., et al., *Age-associated arterial wall thickening is related to elevations in sympathetic activity in healthy humans.* Am J Physiol Heart Circ Physiol, 2000. **278**(4): p. H1205-10.

83. Tanaka, H., et al., *Carotid artery wall hypertrophy with age is related to local systolic blood pressure in healthy men.* Arterioscler Thromb Vasc Biol, 2001. **21**(1): p. 82-7.

84. Pignoli, P., et al., *Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging.* Circulation, 1986. **74**(6): p. 1399-406.

85. Monahan, K.D., et al., *Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance.* Am J Physiol Heart Circ Physiol, 2001. **281**(1): p. H284-9.

86. Corretti, M.C., et al., *Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force.* J Am Coll Cardiol, 2002. **39**(2): p. 257-65.

87. Tanaka, H., *Effects of cross-training. Transfer of training effects on VO2max between cycling, running and swimming.* Sports Med, 1994. **18**(5): p. 330-339.

88. Wang, K.-L., et al., *Central or peripheral systolic or pulse pressure: which best relates to target-organs and future mortality?* Journal of hypertension, 2009. **27**(3): p. 461.

89. Williams, B., et al., *Differential impact of blood pressure–lowering drugs on central aortic pressure and clinical outcomes principal results of the Conduit*

Artery Function Evaluation (CAFE) Study. Circulation, 2006. **113**(9): p. 1213-1225.

90. Zhang, W., et al., *OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence.* Osteoarthritis Cartilage, 2007. **15**(9): p. 981-1000.

91. Yuan, G.H., et al., *Immunologic intervention in the pathogenesis of osteoarthritis.* Arthritis Rheum, 2003. **48**(3): p. 602-11.

92. Sellam, J. and F. Berenbaum, *The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis.* Nat Rev Rheumatol, 2010. **6**(11): p. 625-35.

93. Creamer, P. and M.C. Hochberg, *Osteoarthritis.* The Lancet, 1997. **350**(9076): p. 503-509.

94. Centers for Disease, C. and Prevention, *Prevalence and most common causes of disability among adults--United States, 2005.* MMWR Morb Mortal Wkly Rep, 2009. **58**(16): p. 421-6.

95. Creamer, P. and M.C. Hochberg, *Why does osteoarthritis of the knee hurt--sometimes?* Br J Rheumatol, 1997. **36**(7): p. 726-8.

96. Davis, M.A., et al., *Correlates of knee pain among US adults with and without radiographic knee osteoarthritis.* J Rheumatol, 1992. **19**(12): p. 1943-9.

97. Ulrich-Vinther, M., et al., *Articular cartilage biology.* J Am Acad Orthop Surg, 2003. **11**(6): p. 421-30.

98. Teichtahl, A.J., et al., *Occupational activity is associated with knee cartilage morphology in females.* Maturitas, 2010. **66**(1): p. 72-6.

99. Clark, I.M., et al., *The measurement of collagenase, tissue inhibitor of metalloproteinases (TIMP), and collagenase-TIMP complex in synovial fluids from patients with osteoarthritis and rheumatoid arthritis.* Arthritis Rheum, 1993. **36**(3): p. 372-9.

100. Ishiguro, N., et al., *Relationship of matrix metalloproteinases and their inhibitors to cartilage proteoglycan and collagen turnover: analyses of synovial fluid from patients with osteoarthritis.* Arthritis Rheum, 1999. **42**(1): p. 129-36.

101. Buckwalter, J.A., C. Saltzman, and T. Brown, *The impact of osteoarthritis: implications for research.* Clin Orthop Relat Res, 2004(427 Suppl): p. S6-15.

102. Felson, D.T., et al., *Obesity and knee osteoarthritis. The Framingham Study.* Ann Intern Med, 1988. **109**(1): p. 18-24.

103. Yusuf, S., et al., *Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization.* Circulation, 2001. **104**(22): p. 2746-53.

104. Yusuf, S., et al., *Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies.* Circulation, 2001. **104**(23): p. 2855-64.

105. Shiroma, E.J. and I.M. Lee, *Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity.* Circulation, 2010. **122**(7): p. 743-52.

106. Li, J. and J. Siegrist, *Physical activity and risk of cardiovascular disease--a meta-analysis of prospective cohort studies.* Int J Environ Res Public Health, 2012. **9**(2): p. 391-407.

107. Landi, F., et al., *Disability, more than multimorbidity, was predictive of mortality among older persons aged 80 years and older.* J Clin Epidemiol, 2010. **63**(7): p. 752-9.

108. Rahman, M.M., et al., *Risk of cardiovascular disease in patients with osteoarthritis: a prospective longitudinal study.* Arthritis Care Res (Hoboken), 2013. **65**(12): p. 1951-8.

109. Watson, D.J., T. Rhodes, and H.A. Guess, *All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database.* J Rheumatol, 2003. **30**(6): p. 1196-202.

110. Tanuseputro, P., et al., *Risk factors for cardiovascular disease in Canada.* Can J Cardiol, 2003. **19**(11): p. 1249-59.

111. van Leuven, S.I., et al., *Systemic inflammation as a risk factor for atherothrombosis.* Rheumatology (Oxford), 2008. **47**(1): p. 3-7.

112. Hansson, G.K. and A. Hermansson, *The immune system in atherosclerosis.* Nat Immunol, 2011. **12**(3): p. 204-12.

113. Ross, R., *Atherosclerosis--an inflammatory disease.* N Engl J Med, 1999. **340**(2): p. 115-26.

114. Libby, P., *Inflammation and cardiovascular disease mechanisms.* Am J Clin Nutr, 2006. **83**(2): p. 456S-460S.

115. Hochberg, M.C., *Mortality in osteoarthritis.* Clin Exp Rheumatol, 2008. **26**(5 Suppl 51): p. S120-4.

116. Arnett, D.K., G.W. Evans, and W.A. Riley, *Arterial stiffness: a new cardiovascular risk factor?* Am J Epidemiol, 1994. **140**(8): p. 669-82.

117. Riley, W.A., et al., *Decreased arterial elasticity associated with cardiovascular disease risk factors in the young. Bogalusa Heart Study.* Arteriosclerosis, 1986. **6**(4): p. 378-86.

118. Hodes, R.J., E.G. Lakatta, and C.T. McNeil, *Another modifiable risk factor for cardiovascular disease? Some evidence points to arterial stiffness.* J Am Geriatr Soc, 1995. **43**(5): p. 581-2.

119. Laurent, S., et al., *Expert consensus document on arterial stiffness: methodological issues and clinical applications.* Eur Heart J, 2006. **27**(21): p. 2588-605.

120. Mitchell, G.F., et al., *Arterial stiffness and cardiovascular events: the Framingham Heart Study.* Circulation, 2010. **121**(4): p. 505-11.

121. Sutton-Tyrrell, K., et al., *Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition.* Hypertension, 2001. **38**(3): p. 429-33.

122. Monahan, K.D., et al., *Central arterial compliance is associated with age- and habitual exercise-related differences in cardiovagal baroreflex sensitivity.* Circulation, 2001. **104**(14): p. 1627-32.

123. Monahan, K.D., et al., *Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance.* American Journal of Physiology-Heart and Circulatory Physiology, 2001. **281**(1): p. H284-H289.

124. Nitta, K., et al., *Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients.* Hypertens Res, 2004. **27**(1): p. 47-52.

125. Kelly, R., et al., *Noninvasive determination of age-related changes in the human arterial pulse.* Circulation, 1989. **80**(6): p. 1652-9.

126. Nichols, W., M. O'Rourke, and C. Vlachopoulos, *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*. 2011: CRC Press.

127. Boutouyrie, P., et al., *Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study.* Hypertension, 2002. **39**(1): p. 10-5.

128. Vlachopoulos, C., K. Aznaouridis, and C. Stefanadis, *Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis.* J Am Coll Cardiol, 2010. **55**(13): p. 1318-27.

129. Taddei, S., et al., *Age-related reduction of NO availability and oxidative stress in humans.* Hypertension, 2001. **38**(2): p. 274-9.

130. Celermajer, D.S., et al., *Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction.* J Am Coll Cardiol, 1994. **24**(6): p. 1468-74.

131. Yeboah, J., et al., *Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study.* Circulation, 2007. **115**(18): p. 2390-7.

132. Messier, S.P., et al., *Exercise and weight loss in obese older adults with knee osteoarthritis: a preliminary study.* J Am Geriatr Soc, 2000. **48**(9): p. 1062-72.

133. Spector, T.D., et al., *Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease.* Arthritis Rheum, 1997. **40**(4): p. 723-7.

134. Goldring, M.B. and M. Otero, *Inflammation in osteoarthritis.* Curr Opin Rheumatol, 2011. **23**(5): p. 471-8.

135. Sharif, M., et al., *Increased serum C reactive protein may reflect events that precede radiographic progression in osteoarthritis of the knee.* Ann Rheum Dis, 2000. **59**(1): p. 71-4.

136. Penninx, B.W., et al., *Physical exercise and the prevention of disability in activities of daily living in older persons with osteoarthritis.* Arch Intern Med, 2001. **161**(19): p. 2309-16.

137. Lakatta, E.G. and D. Levy, *Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease.* Circulation, 2003. **107**(2): p. 346-54.

138. Zieman, S.J., V. Melenovsky, and D.A. Kass, *Mechanisms, pathophysiology, and therapy of arterial stiffness.* Arterioscler Thromb Vasc Biol, 2005. **25**(5): p. 932-43.

139. Barnes, J.N., et al., *Arterial stiffening, wave reflection, and inflammation in habitually exercising systemic lupus erythematosus patients.* American journal of hypertension, 2011. **24**(11): p. 1194-1200.

140. Crilly, M.A., et al., *Arterial stiffness and cumulative inflammatory burden in rheumatoid arthritis: a dose-response relationship independent of established cardiovascular risk factors.* Rheumatology (Oxford), 2009. **48**(12): p. 1606-12.

141. Cypiene, A., et al., *The impact of systemic sclerosis on arterial wall stiffness parameters and endothelial function.* Clin Rheumatol, 2008. **27**(12): p. 1517-22.

142. Rollando, D., et al., *Brachial artery endothelial-dependent flow-mediated dilation identifies early-stage endothelial dysfunction in systemic sclerosis and correlates with nailfold microvascular impairment.* J Rheumatol, 2010. **37**(6): p. 1168-73.

143. Carson, J.L., et al., *The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding.* Archives of Internal Medicine, 1987. **147**(1): p. 85-88.

144. Carson, J.L., et al., *The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding.* Arch Intern Med, 1987. **147**(1): p. 85-8.

145. Batterham, S.I., S. Heywood, and J.L. Keating, *Systematic review and meta-analysis comparing land and aquatic exercise for people with hip or knee arthritis*

on function, mobility and other health outcomes. BMC musculoskeletal disorders, 2011. **12**(1): p. 123.

146. Fransen, M. and S. McConnell, *Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials.* J Rheumatol, 2009. **36**(6): p. 1109-17.

147. Bartels, E.M., et al., *Aquatic exercise for the treatment of knee and hip osteoarthritis.* Cochrane Database Syst Rev, 2007(4): p. CD005523.

148. Creamer, P. and M.C. Hochberg, *Osteoarthritis.* Lancet, 1997. **350**(9076): p. 503-8.

149. Kaneko, Y., H. Kondo, and T. Takeuchi, *American College of Rheumatology/European League Against Rheumatism remission criteria for rheumatoid arthritis maintain reliable performance when evaluated in 44 joints.* J Rheumatol, 2013. **40**(8): p. 1254-8.

150. Jansen, M.J., et al., *Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: a systematic review.* J Physiother, 2011. **57**(1): p. 11-20.

151. Fransen, M. and S. McConnell, *Exercise for osteoarthritis of the knee.* Cochrane Database Syst Rev, 2008(4): p. CD004376.

152. Roddy, E., W. Zhang, and M. Doherty, *Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review.* Ann Rheum Dis, 2005. **64**(4): p. 544-8.

153. Pelland, L., et al., *Efficacy of strengthening exercises for osteoarthritis (part I): a meta-analysis.* Physical therapy reviews, 2004. **9**(2): p. 77-108.

154. Jan, M.H., et al., *Effects of weight-bearing versus nonweight-bearing exercise on function, walking speed, and position sense in participants with knee osteoarthritis: a randomized controlled trial.* Arch Phys Med Rehabil, 2009. **90**(6): p. 897-904.

155. Tanaka, R., et al., *Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials.* Clin Rehabil, 2013. **27**(12): p. 1059-71.

156. Barker, A.L., et al., *Effectiveness of aquatic exercise for musculoskeletal conditions: a meta-analysis.* Arch Phys Med Rehabil, 2014. **95**(9): p. 1776-86.

157. Juhl, C., et al., *Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials.* Arthritis Rheumatol, 2014. **66**(3): p. 622-36.

158. Valderrabano, V. and C. Steiger, *Treatment and prevention of osteoarthritis through exercise and sports. J Aging Res. 2011. ID 374653*.

159. Pate, R.R., et al., *Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine.* JAMA, 1995. **273**(5): p. 402-7.

160. Belza, B.L., et al., *Correlates of fatigue in older adults with rheumatoid arthritis.* Nurs Res, 1993. **42**(2): p. 93-9.

161. Arnett, F.C., et al., *The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis.* Arthritis Rheum, 1988. **31**(3): p. 315-24.

162. Bauman, A.E., *Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003.* J Sci Med Sport, 2004. **7**(1 Suppl): p. 6-19.

163. Avina-Zubieta, J.A., et al., *Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies.* Arthritis Rheum, 2008. **59**(12): p. 1690-7.

164. Tanaka, H., *Swimming exercise: impact of aquatic exercise on cardiovascular health.* Sports Med, 2009. **39**(5): p. 377-87.

165. Levy, C., E. Kolin, and B. Berson, *Cross training: risk or benefit? An evaluation of injuries in four athlete populations.* Sports Med, 1986. **3**: p. 1-8.

166. Froelicher, V.F., *Exercise testing and training: clinical applications.* Journal of the American College of Cardiology, 1983. **1**(1): p. 114-125.

167. Tanaka, H., et al., *Swimming training lowers the resting blood pressure in individuals with hypertension.* J Hypertens, 1997. **15**(6): p. 651-7.

168. Bureau, C., *Statistical abstract of the United States.* 2009.

169. Buskirk, E.R. and S.M. Puhl, *Body fluid balance: exercise and Sport*. Vol. 9. 1996: CRC Press.

170. Jost, J., M. Weiss, and H. Weicker, *Sympathoadrenergic regulation and the adrenoceptor system.* J Appl Physiol (1985), 1990. **68**(3): p. 897-904.

171. Marconnet, P., et al., *Preexercise, exercise and early post exercise arterial blood pressure in young competitive swimmers versus non swimmers.* J Sports Med Phys Fitness, 1984. **24**(3): p. 252-8.

172. Cureton, T.K. and F.W. Kasch, *Physical fitness appraisal and guidance*. 1947: Mosby.

173. Holmer, I., et al., *Hemodynamic and respiratory responses compared in swimming and running.* J Appl Physiol, 1974. **37**(1): p. 49-54.

174. Cox, K.L., et al., *Blood pressure rise with swimming versus walking in older women: the Sedentary Women Exercise Adherence Trial 2 (SWEAT 2).* J Hypertens, 2006. **24**(2): p. 307-14.

175. Zinman, B., et al., *Physical activity/exercise and diabetes mellitus.* Diabetes Care, 2003. **26 Suppl 1**: p. S73-7.

176. Cleroux, J., R.D. Feldman, and R.J. Petrella, *Lifestyle modifications to prevent and control hypertension. 4. Recommendations on physical exercise training. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada.* CMAJ, 1999. **160**(9 Suppl): p. S21-8.

177. Haskell, W.L., et al., *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association.* Med Sci Sports Exerc, 2007. **39**(8): p. 1423-34.

178. Meyer, K. and M.C. Leblanc, *Aquatic therapies in patients with compromised left ventricular function and heart failure.* Clin Invest Med, 2008. **31**(2): p. E90-7.

179. Booth, M.L., et al., *Physical activity preferences, preferred sources of assistance, and perceived barriers to increased activity among physically inactive Australians.* Prev Med, 1997. **26**(1): p. 131-7.